Cardiovascular implantable electronic devices

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CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES
THE PATIENT PERSPECTIVE

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CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES
THE PATIENT PERSPECTIVE

Proefschrift

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TABLE OF CONTENTS

Chapter 1

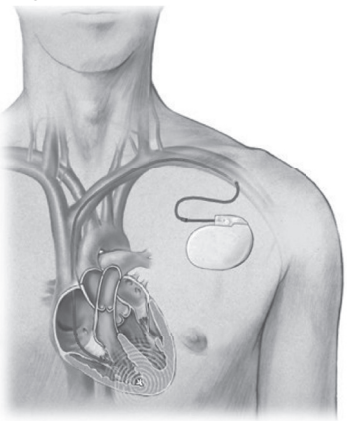
General introduction

CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

Cardiovascular implantable electronic devices, such as the implantable cardioverter defibrillator (ICD) and the biventricular pacemaker providing cardiac resynchronization therapy (CRT), used either alone or in combination (i.e., CRT-defibrillator or CRT-D), have gained increasing acceptance and are now implemented on a large scale in subgroups of patients with heart disease.[1] Currently, more than 800.000 patients in Europe are living with an implantable electronic device and this number is expected to increase in the future.[2]

ICD and CRT treatment: How does it work?

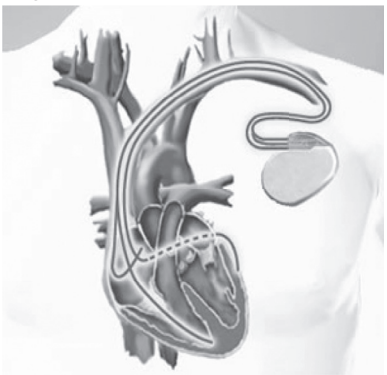
Figure 1. ICD[3]



The ICD (Figure 1) continuously monitors the rhythm of the heart for the occurrence of life-threatening tachyarrhythmias originating in the right or left ventricle. During a ventricular tachycardia (VT) the rhythm is accelerated, often resulting in a reduced pumping function of the heart. This causes a drop in blood pressure leading to dizziness or loss of consciousness. An untreated VT can deteriorate into ventricular fibrillation (VF) – a cardiac arrest with an electrical chaos in the ventricles making them quiver rather than contract properly – which without prompt intervention will almost always lead to sudden cardiac death (SCD). VFs can also have a sudden onset, e.g. during myocardial ischemia. SCDs account for approximately 50% of all deaths from cardiovascular disease,[4] with about 80-90% of these deaths being attributable to ventricular tachyarrhythmias.[5] In case of sustained VT, the ICD uses anti-tachycardia pacing (ATP), which involves short bursts of pacing impulses at faster rates than the tachycardia, or low energy shocks (cardioversion) to prevent progression into VF.[6] When ATP and cardioversion are unsuccessful or in case of sudden-onset VF, the ICD can deliver immediate defibrillation by high-energy shocks (up to 800 volts) to restore normal heart rhythm.[6]

CRT is indicated for a subgroup of patients with congestive heart failure (CHF), which is a chronic and debilitating disease characterized by symptoms of tiredness and shortness of breath, and signs of peripheral and/or lung edema, arising as a consequence of a structural or functional abnormality of the heart.[7] The prevalence of CHF in the Western world is estimated at 2-3%.[8,9] In the 51 countries that fall under the European Society of Cardiology, there are at least 15 million people with CHF,[8] and this number is expected to increase in the future due to the ageing of the population and improved survival of cardiac patients.[10,11] Mortality and morbidity rates are high,[12,13] and only 25-35% of CHF patients survive beyond 5 years following diagnosis.[14,15]

Figure 2. CRT



In approximately one third of patients with CHF, the electrocardiogram (ECG) shows a prolonged QRS interval (>120 ms), indicating that the depolarization of the ventricles is delayed.[16] This can be a result of a left or right bundle branch block or a nonspecific intraventricular conduction delay, leading to disruption of the normal, coordinated and simultaneous distribution of the electrical signal to the two ventricles. This may further impair the already diminished ventricular ejection fraction (i.e., the fraction of blood pumped out of the ventricles with each heart beat).[17] CRT – or biventricular pacing – is intended to modulate the inter-/intraventricular conduction delay by simultaneously pacing both ventricles. CRT devices (Figure 2) have at least two leads, one in the right ventricle and another inserted through the coronary sinus to pace the lateral free wall of the left ventricle. For patients in normal sinus rhythm, there is also a lead in the right atrium to facilitate synchrony with the atrial contraction. As ventricular tachyarrhythmias are common in CHF patients,[18] CRT is often combined with ICD therapy (i.e., CRT-D).

Expanding indications and implantation rates

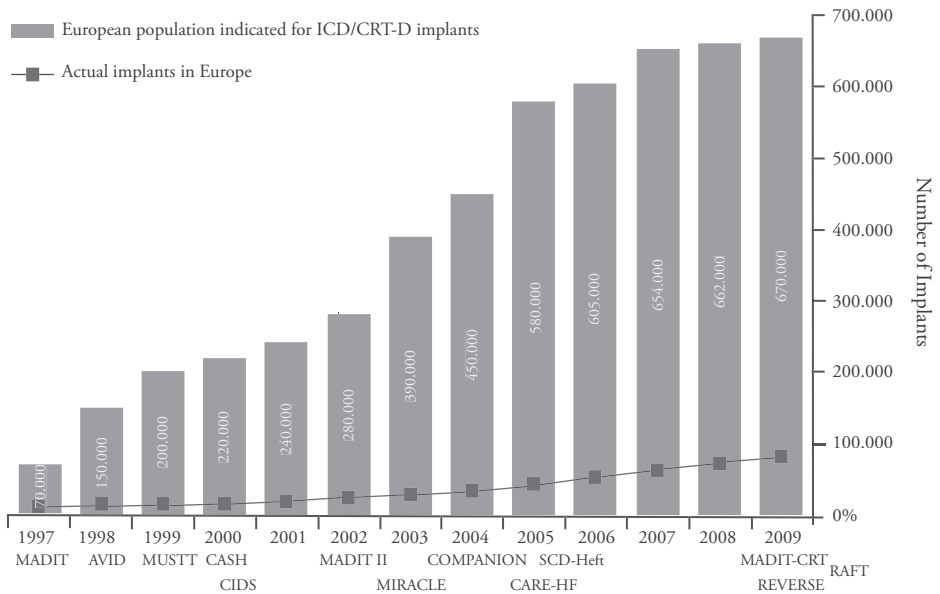
ICD therapy was initially only indicated as secondary prevention in patients who had survived an initial sudden cardiac arrest. The landmark secondary prevention trials, such as the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, the Canadian Implantable Defibrillator Study (CIDS) and the Cardiac Arrest Study Hamburg (CASH), showed a significant reduction in mortality (28%) with ICD therapy compared to antiarrhythmic drugs, which was almost entirely due to a 50% reduction in arrhythmic death.[19] With the widespread acceptance of the ICD for the secondary prevention of SCD and the change from epicardial to transvenous ICD implantation, attention turned to the usefulness of the ICD for primary prevention of SCD in patients with left ventricular dysfunction who did not experience prior life-threatening arrhythmias but are considered at high risk. A series of primary prevention trials, e.g., the Multicenter Automatic Defibrillator Implantation Trial (MADIT(-II)) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), demonstrated a significant reduction in mortality (26%) with the ICD.[20] Hence, ICD indications have expanded from secondary prevention to also include primary prevention of SCD.

From 2001 onwards, several large-scale randomized clinical trials, e.g., the Multicenter InSyncRandomized Clinical Evaluation (MIRACLE) trial, the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial and the Cardiac Resynchronization-Heart Failure (CARE-HF) trial, have shown that CRT leads to improvements in CHF symptoms, functional

capacity and left ventricular function, and reduced mortality and hospitalization in patients with moderate to severe heart failure symptoms (New York Heart Association (NYHA) functional class III or IV) despite optimal pharmacological therapy, with a depressed left ventricular ejection fraction of ≤35% and a prolonged QRS interval of ≥120ms.[21,22] CRT(-D) is recommended as a class I indication, level A evidence, as a means to improve prognosis in these patients.[8] In 2010, the indications for CRT were expanded to also include mildly symptomatic CHF patients (NYHA functional class II) on optimal pharmacological therapy, with a left ventricular ejection fraction ≤35% and a QRS duration ≥150 ms, in order to reduce morbidity and slow down disease progression.[23] This recommendation is based on the results of recent trials, i.e., the MADIT-CRT, the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, and the Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT), showing that CRT(-D) therapy is beneficial in patients with mild CHF symptoms.[24-26] Despite large-scale studies demonstrating that the majority of patients benefit from CRT, a significant proportion (10-40%) of patients do not respond to this treatment and are considered nonresponders. No clear consensus regarding the definition of a positive response to CRT exists,[27] and the mechanisms responsible for benefits versus no benefits are not fully understood.[28]

Based on the criteria in the major trials, the number of patients in Europe indicated for ICD or CRT therapy has steadily increased over time, but only a fraction (12%) of these patients are actually implanted with an ICD or CRT device (Figure 3).

Figure 3. Percentage of patients fulfilling the criteria for the major ICD/CRT(-D) trials, which actually get implanted in Western Europe



Based on data from EUCOMED and European guidelines.[29,30]

THE PATIENT PERSPECTIVE

Living with a cardiovascular implantable electronic device

Device therapy is a state-of-the-art medical technology which is continuously evolving and is associated with a range of challenges for patients. Besides dealing with their life-threatening condition, ICD/CRT(-D) patients have to live with the risk of procedural and device-related complications, such as infection and lead dislocation, potential hardware malfunctioning leading to advisory notices, and – appropriate and inappropriate – ICD shocks. Inappropriate shocks refer to the device giving a shock although in fact no life-threatening arrhythmia occurred. These issues may all have a negative impact on morbidity and mortality, but also on the psychological functioning and quality of life of patients.[31,32]

Although device therapy is well tolerated by the majority of patients, a subset of patients with an ICD/CRT-D report heightened psychological distress and impaired health status following implantation.[33-35] Health status refers to the patient's perception of how a disease or treatment affects his/her function, symptoms, and quality of life, with quality of life being the discrepancy between actual and desired function.[36,37] The most common psychological problems reported by ICD patients are depression, anxiety and specific device- or disease-related concerns such as fear of ICD shocks, device malfunction, and fear of death.[38,39] Depressive symptoms are experienced by 24-33% of the ICD recipients.[38] Anxiety is more prevalent, with studies indicating that approximately 24-87% of ICD recipients report increased levels of anxiety post implantation, with 13-38% meeting diagnostic criteria for an anxiety disorder such as posttraumatic stress disorder.[38,40]

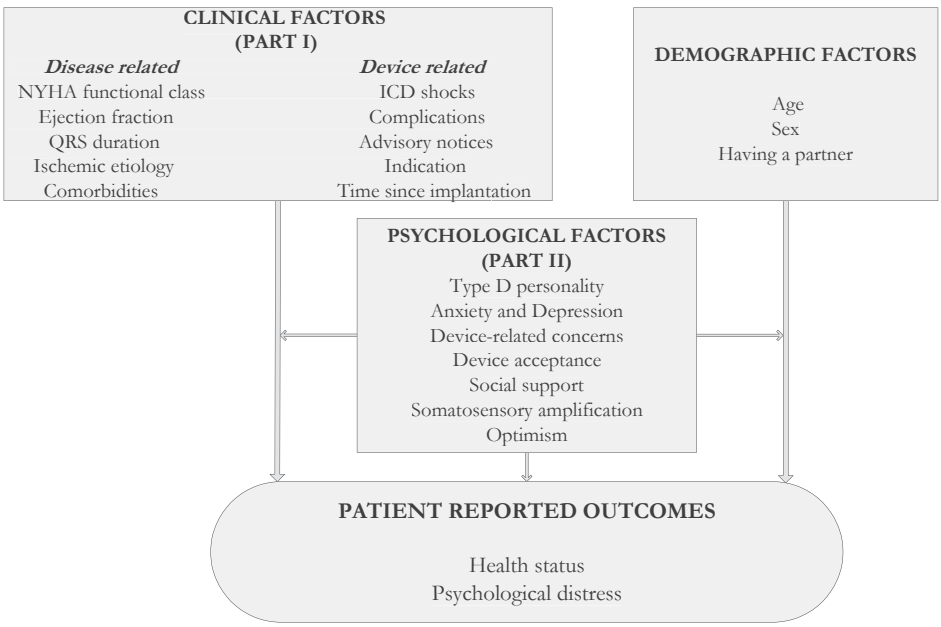
The importance of examining the patient perspective and its determinants

Patient reported outcomes are receiving increased recognition as important cardiovascular endpoints in clinical trials and are recommended as performance measures of high quality care, as they offer physicians insight into their patient's physical and psychological needs and may guide clinical decision making.[36,41] They are essential for patient centered care, as patients want to know how a treatment will affect their symptoms, function, and quality of life, particularly because some patients may prefer a better health status over prolonged survival.[42,43] Besides being important outcome measures and key components of patient centered care, patient reported outcomes are important for secondary prevention. Poor patient health status and psychological distress have been associated with increased risk of mortality and hospital admissions in CHF and ICD patients,[44-47] and also with the onset of ventricular tachyarrhythmias in ICD patients,[48,49] independent of indicators of disease severity.

There is a significant gap in our understanding of the determinants of patient reported outcomes.[50] Research has shown that the physician's evaluation of the patient's health,[51] and objective indicators of disease severity,[52,53] are only marginally associated

with the health status as reported by patients. Also, the evidence on the influence of age,[33] sex,[54] ICD shocks,[55] indication (primary versus secondary prevention),[56] and advisory notices[57] on patient reported outcomes is mixed. This raises the question whether psychological factors, such as personality factors, e.g., the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition), pre-implantation ICD concerns, or lack of social support,[58-63] might influence the relationship between obvious device- and disease-related factors and patient reported outcomes in ICD/CRT(-D) patients. Figure 4 provides an overview of the clinical, demographic, and psychological factors that might be or have been associated with patient reported outcomes in ICD and/or CRT(-D) patients. It is essential to know the determinants of patient reported outcomes, in order to identify high-risk patients who may not benefit optimally from device therapy and might need additional treatment.

Figure 4. Clinical, demographic and psychological associates of patient reported outcomes



AIMS AND OUTLINE OF THIS DISSERTATION

The current dissertation focuses on the patient perspective on cardiovascular implantable electronic device therapy. Some of the potential clinical (disease- and device-related) versus psychological associates of patient reported outcomes following ICD/CRT(-D) implantation are examined in order to get a clearer picture of their relative importance.

Part one: The impact of disease- and device-related factors

The first part of this dissertation addresses the impact of disease- and device-related factors on patient reported outcomes in ICD/CRT patients. The first three chapters discuss the association between patient health status and established physician-rated indicators of disease severity in CRT patients. *Chapter 2* provides an overview of these traditional indices currently used to determine response to CRT and discusses their agreement with changes in patient perceived health following implantation based on analysis of the existing literature and case reports. The next two chapters elaborate on this topic and focus on the NYHA functional class, which is used as a measure of the physician's impression of the presence and severity of symptoms and functional limitations in patients with CHF. Results of a multicenter prospective study examining the influence of baseline NYHA functional class (II versus III) on change in patient reported health status in the first 12 months after CRT-D are presented in *Chapter 3*. Next, the study described in *Chapter 4* examines the association between improvement in NYHA functional class and patient reported health status in the first 2 months after CRT implantation in a sample of patients recruited from the University Medical Center Utrecht, the Netherlands.

Besides indices of disease severity, device-related factors such as advisory notices and ICD shocks might influence patient reported outcomes in ICD/CRT-D patients. There is a paucity of research on the psychological impact of device advisory notices, and evidence is mixed. Little is also known about the best way of communicating the risk associated with an advisory to patients. Hence, *Chapter 5* evaluates whether the Sprint Fidelis advisory and the mode used to inform patients about the associated risks influences psychological distress, device related concerns, health status, and device acceptance as reported by a sample of Danish ICD patients. Yet even without complications, ICD treatment may qualify as a potential traumatic stressor as it is a constant reminder of the underlying life-threatening condition and is able to deliver an uncontrollable shock. The prevalence and determinants of posttraumatic stress symptoms in a sample of 300 ICD patients implanted at the Erasmus Medical Center, Rotterdam, the Netherlands, are outlined in *Chapter 6*.

Part two: The importance of psychological factors

In addition to disease- and device-related factors, psychological factors could play a role in determining patients reported outcomes in ICD/CRT patients and might explain why some patients do not benefit from cardiovascular implantable electronic device therapy. *Chapter 7* reports on a study in German ICD patients investigating whether somatosensory amplification – the tendency to be more aware of and attentive to weak or diffuse bodily sensations and to appraise them as abnormal and symptomatic of disease – could explain why female patients might report more psychological distress following implantation than males. Also, personality factors might influence differences

in patient reported health outcomes. For example, accumulating evidence has shown that Type D personality is associated with adverse health outcomes. A meta-analysis of studies evaluating the influence of Type D personality on patient reported physical and mental health status in cardiovascular patients is presented in *Chapter 8*. Distress levels in patients could even be related to partner factors leading to poor communication and lack of social support. In *Chapter 9*, the impact of the personality of the partner (i.e., Type D personality) in combination with that of the patient on anxiety and depression levels in ICD patients is addressed. Another psychological factor that might be essential in identifying patients at risk for adverse outcomes, is poor device acceptance – which refers to the psychological accommodation and understanding of the device and the derivation of benefit in terms of biopsychosocial functioning. The Florida Patient Acceptance Scale (FPAS) is one of the few instruments available to measure ICD acceptance. In *Chapter 10*, the psychometric properties of the FPAS and correlates of device acceptance are examined in a cohort of Dutch ICD patients.

In *Chapter 11* the main findings of this dissertation will be discussed and implications for future research and clinical practice will be outlined.

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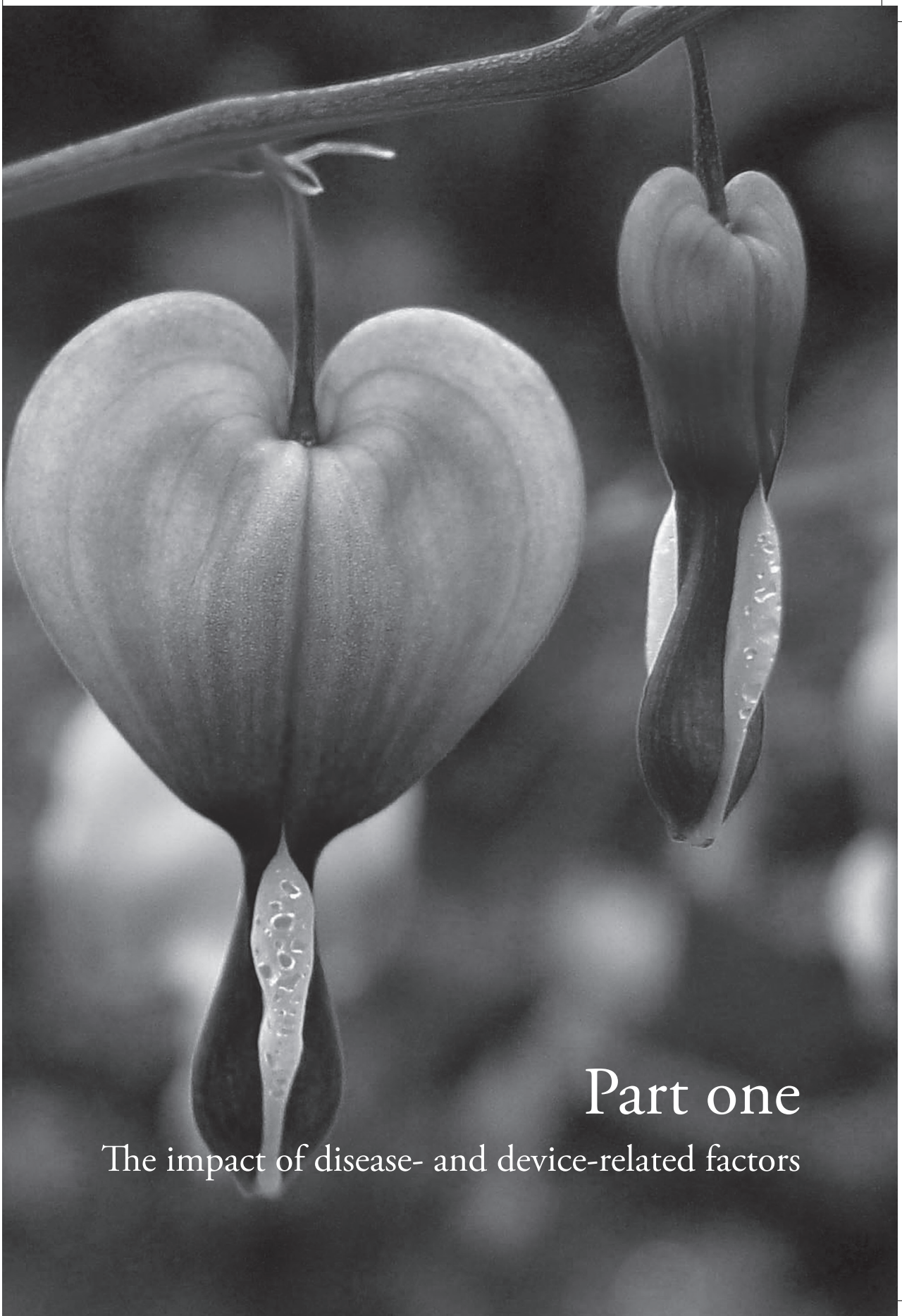
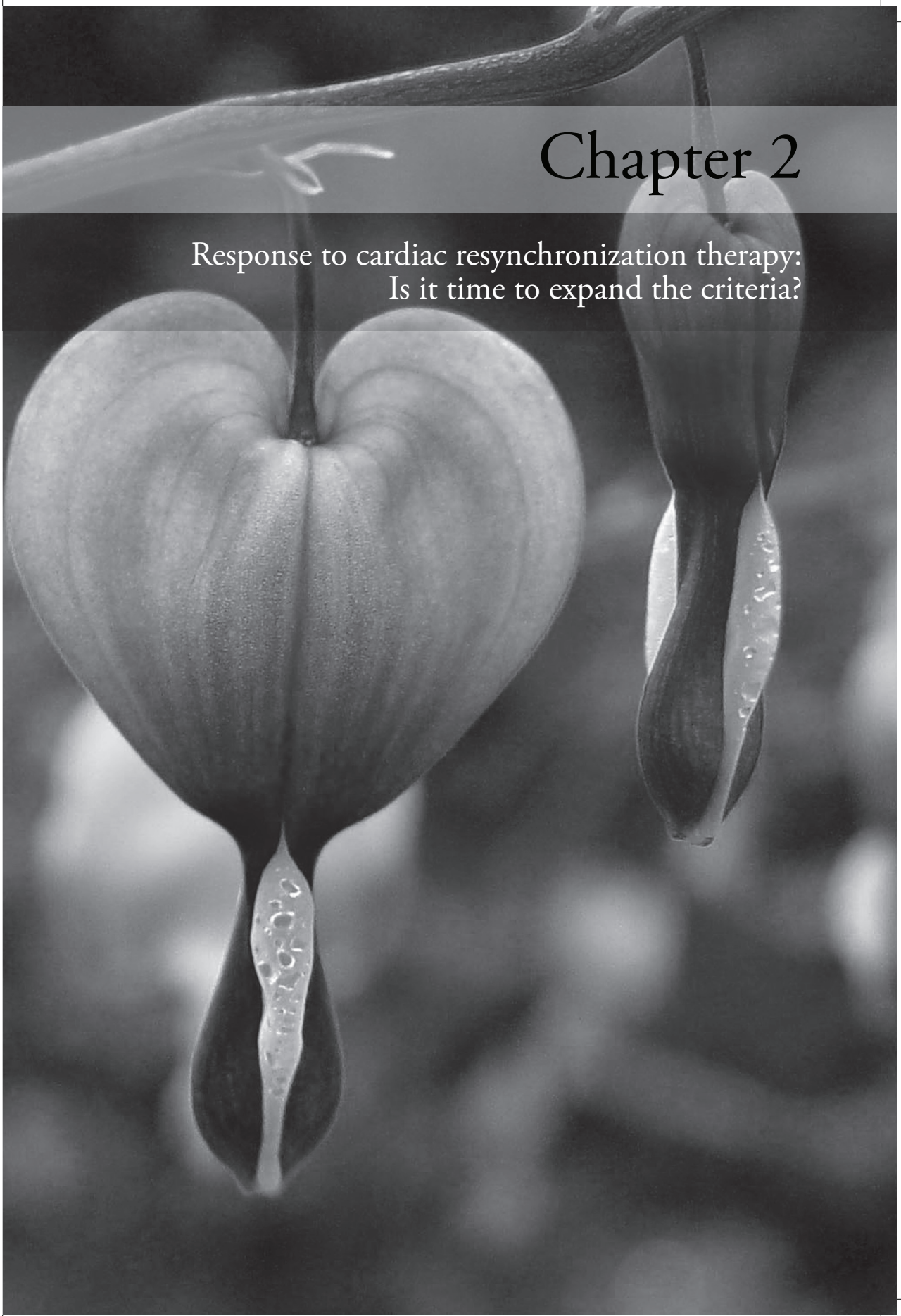


Part one

The impact of disease- and device-related factors



Chapter 2

Response to cardiac resynchronization therapy: Is it time to expand the criteria?

ABSTRACT

Background Cardiac resynchronization therapy (CRT) is a promising treatment for a subgroup of patients with advanced congestive heart failure (CHF) and a prolonged QRS interval. Despite the majority of patients benefiting from CRT, 10% to 40% of patients do not respond to this treatment, labeled as nonresponders. Given that there is a lack of consensus on how to define response to CRT, the purpose of this viewpoint is to discuss currently used definitions and their shortcomings, and to provide recommendations as to how an expansion of the criteria for CRT response may be useful to clinicians.

Methods and Results Analysis of the literature and case reports indicates that the majority of established measures of CRT response, including New York Heart Association (NYHA) functional class and echocardiographic, hemodynamic, and neurohormonal parameters, are poor associates of patient reported symptoms and quality of life. Moreover, the potential moderating role of psychological factors in determining health outcomes after CRT has largely been neglected.

Conclusions It is recommended to routinely assess health status after CRT with a disease-specific questionnaire in standard clinical practice and to examine its determinants, including psychological factors such as personality traits and depression. This may lead to improved (secondary) treatment and prognosis in CHF patients treated with CRT.

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INTRODUCTION

Congestive heart failure (CHF) is a debilitating and persistent clinical syndrome, typified by symptoms of tiredness and breathlessness, and signs of tachypnoea and hepatomegaly, in addition to objective evidence of a structural or functional abnormality of the heart at rest.[1,2] In the United States, approximately 5 million people have CHF,[3] and of the more than 900 million people living in the countries that fall under the European Society of Cardiology, at least 15 million people have the disease.[1] Despite important advances in medical therapy, mortality and morbidity rates are still high.[4,5]

Cardiac resynchronization therapy (CRT) is a promising treatment for a subgroup of patients with advanced CHF and a prolonged QRS interval.[6,7] This inter-/intraventricular conduction delay is recognizable on the electrocardiogram as a bundle branch block which may further impair the ventricular ejection fraction.[8] The precise mechanisms underlying the benefits of CRT are not clear, but appear to be related to modulation of the conduction delay which can optimize contractile synchrony, improve systolic function and reduce mitral regurgitation.[9] Especially patients with a QRS duration ≥155 ms and depressed left ventricular pressure rise (dP/dtmax ≤700 mmHg/s) should show the greatest improvement with CRT.[10] Although studies have shown that only patients with left bundle branch block (LBBB) benefit from CRT,[11] no distinction is made between the sides of electrical block in the current guidelines.[1]

CRT has been shown to improve quality of life and functional status, and to reduce mortality and morbidity.[12,13] Therefore, CRT has been used extensively over the last years in patients with end-stage CHF who remain symptomatic (New York Heart Association (NYHA) functional class III-IV) despite optimal pharmacological therapy, have a depressed left ventricular function (left ventricular ejection fraction (LVEF) <35%), and a prolonged QRS interval (>120 ms). In the most recent guidelines for CHF, CRT is recommended as a class I indication, level A evidence, as a means to improve prognosis in these patients.[1] Despite large-scale studies demonstrating that the majority of patients benefit from CRT, a significant proportion of patients do not respond to this treatment, labeled as nonresponders.[12,14] A complicating factor in this context is that there is a lack of consensus on how to define response to CRT. In studies using a composite score of subjective and/or objective measures of clinical status (e.g. NYHA class, quality of life, hospitalization, and mortality), 11-33% of the patients were classified as nonresponders after 6 months of CRT.[6,15,16] In recent echocardiographic studies, the percentage of nonresponders was even larger; no positive response, defined as a reduction of ≥15% in left ventricular end-systolic volume (LVESV), was observed in up to 44% of patients.[16,17] The purpose of this viewpoint is to discuss currently used definitions of CRT response and their shortcomings, and to provide recommendations as to how an expansion of the criteria for CRT response may be useful to clinicians.

PROBLEMS WITH THE DEFINITION OF RESPONSE TO CRT

Currently, five types of indices are used to determine CRT response (Table 1): (1) clinical, such as NYHA class and quality of life; (2) functional, for example, oxygen uptake at peak exercise (VO_2max) and the distance walked in 6 minutes (6MWD); (3) echocardiographic, including LVEF and left ventricular end-diastolic and end-systolic volumes (LVEDV, LVESV); (4) hemodynamic, like dP/dt_{max} and the cardiac index; and (5) neurohormonal, for example, B-type natriuretic peptide (BNP) level.[14,18]

Table 1. Traditionally used criteria for assessing response to CRT

	Objective	Subjective
Acute	dP/dt_{max}	
	blood pressure	
	mitral regurgitation	
Chronic	LVEDV, LVESV	NYHA functional class
	LVEF	(physical) quality of life
	mechanical asynchrony	
	QRS duration	
	cardiac index	
	BNP level	
	VO_2max[a]	
	6MWD[a]	

[a] VO_2max and 6MWD are not entirely objective, as they are also dependent on subjective factors such as the motivation of the patient

6MWD=6-minute walking distance; BNP=brain natriuretic peptide; dP/dt_{max}=maximum rate of (left ventricular) pressure rise; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NYHA=New York Heart Association; VO_2max=oxygen uptake at peak exercise.

Appendix I gives an overview of the clinical trials that investigated the effects of CRT on one or more of these indices, compared to optimal medical treatment or implantable cardioverter defibrillator (ICD) therapy, in patients with a class I indication for CRT without atrial fibrillation. The presented results stem from the primary publications of these trials.[6,11,19-25] From this overview, it becomes clear that the trials use different endpoints to assess CRT response and that the results vary widely. But all trials included measures of clinical response, which represents relief of symptoms and improved quality of life. It is the most subjective index of CRT response and one of the most important targets of treatment in patients with CHF.[26] In standard clinical practice, the clinical CRT response is most often defined as an improvement in ≥1 NYHA class, with NYHA class traditionally being used as a measure of the clinician's impression of the presence and severity of symptoms in

CHF patients.[27]

Although NYHA class is associated with prognosis in CHF,[28,29] it has been criticized as a single marker for clinical response, as the method of assignment is not standardized,[30,31] the interrater reliability is poor,[31,32] and there is only a moderate association between clinician assigned NYHA class and patient reported severity of symptoms, quality of life, psychological distress, and life satisfaction.[33-37] In addition, most of the variation in quality of life scores cannot be explained by NYHA class, with the possibility that clinically relevant changes in health status can occur in the absence of changes in NYHA class.[38,39] Therefore, NYHA class cannot be used as a sole outcome measure reflecting clinical CRT response. In addition, NYHA classification is predominantly a measure of functional status,[40] while CHF patients experience not only functional losses but also a variety of psychosocial, socio-economic, and emotional concerns that affect their overall quality of life.[41,42] A more holistic assessment of the symptoms and quality of life of CHF patients is needed in routine clinical care, as it may help improve monitoring and treatment of patients receiving CRT.

Moreover, research indicates that patients' self-reported symptoms and quality of life have unique prognostic value. Studies conducted in CHF patients showed that poor patient reported health status predicts mortality and hospitalization, independent of demographic factors and indicators of disease severity, with the likelihood that this finding may be extrapolated to CRT patients.[43,44] To the best of our knowledge, only one study analyzed quality of life as a predictor of mortality after CRT in a clinical trial. Results showed that the baseline quality of life score predicted pump failure death at 3 months in unadjusted analysis.[45] In adjusted analysis however, quality of life was no longer significant, likely due to the relatively short follow-up period, the small number of events and the use of a generic instead of a disease-specific questionnaire. It is recommended to assess health status with a disease-specific questionnaire, for example the Minnesota Living with Heart Failure questionnaire (MLHFQ) or the Kansas City Cardiomyopathy Questionnaire (KCCQ), as a disease-specific measure seems to have greater prognostic value compared to health status assessed with a generic measure.[44]

The MLHFQ and the KCCQ are self-report scales, with good metric and applicability properties, that adequately reflect change over time in health status.[46] It was found that the KCCQ summary score was more discriminative of change in heart failure status than NYHA classification, 6MWD, the generic Short Form-12 and EuroQol-5D scores, weight, and BNP levels.[47] In sum, the incorporation of health status measures in longitudinal care offers a complete and consistent distillation of patients' health status over time and may optimize secondary prevention.[48] For a more in-depth discussion of the clinical utility of health status assessment in cardiac patients, see a recent seminal paper by Spertus.[48]

Besides shortcomings in the assessment of the clinical CRT response, there is a gap in our understanding of its determinants.[49] Research has shown that the severity of cardiac dysfunction as measured by echocardiographic and hemodynamic measures is only marginally associated with clinical health outcomes such as heart failure symptoms,[50] quality of life,[35] and NYHA class.[7] Recent results of large prospective, multicenter trials showed that various echocardiographic measures of ventricular dyssynchrony and LV volume were unable to distinguish between patients who showed improvement of ≥1 NYHA class and those who did not after 6 months of CRT.[16,51] Two studies reported a disagreement between the echocardiographic response, defined as >15% reduction in LVESV or ≥15% relative increase in LVEF, and the clinical response (an improvement by ≥1 NYHA class) in 24-27% of the patients treated with CRT.[52,53] To illustrate this discrepancy between clinical and echocardiographic and hemodynamic CRT responses, we report two cases seen in our clinical practice:

Case 1: The patient is a 62-year old man with a history of anteroseptal myocardial infarction who had NYHA class III-IV CHF due to ischemic cardiomyopathy and a LBBB with a QRS duration of 140 ms. At the time of implantation of the CRT-device with an ICD, that is a CRT-D, his LVEF was 24%, BNP level 249 pmol/L, and VO_2max 14.8 ml/kg/min. Six months after the implantation, there was no echocardiographic or functional response, as there was no reverse remodeling with the left ventricle still dilated with 7.2 cm, an LVEF of 22%, and a paced QRS duration of 160 ms. The BNP level had increased to 265 pmol/L and the VO_2max was even lower than prior to implantation at 12.4 ml/kg/min. However, the patient reported that he felt much better since the implantation and had improved to NYHA class II-III. The patient could perform more physical exertion and was no longer short of breath during daily activities.

Case 2: The patient is a 76-year old woman with a history of dilated cardiomyopathy and an out of hospital cardiac arrest due to ventricular fibrillation for which an ICD was implanted. Because of worsening of CHF symptoms to NYHA class III despite optimal medical treatment, an LVEF of 25%, an LBBB with a QRS duration of 190 ms, and a BNP level of 155 pmol/L, the ICD was upgraded to an CRT-D. Six months after the upgrade, there was a significant improvement in echocardiographic parameters, with a significant decrease in left ventricular end-diastolic diameter from 6.7 to 5.1 cm, an increase in LVEF to 31%, a decrease in QRS duration to 150 ms, and in BNP levels to 71 pmol/L. Despite these echocardiographic and neurohormonal responses, the patient reported no improvement in CHF symptoms. The patient was still classified as NYHA class III, as she still suffered from fatigue and shortness of breath during ordinary daily activities.

These case reports and previous study results indicate that the clinical CRT response cannot be fully explained by changes in established echocardiographic, neurohormonal, and hemodynamic parameters. The presence of a clinical response

without objective improvement might be attributed to a placebo effect, although we cannot rule out the influence of other factors, in particular because some patients do not feel better despite echocardiographic or hemodynamic responses. Numerous studies have been conducted to determine the value of other parameters in predicting clinical CRT (non)response, for instance, intraventricular dyssynchrony measured by tissue Doppler imaging,[17,54] total scar burden,[55] and left ventricular lead electrical delay.[56]

THE ROLE OF PSYCHOLOGICAL FACTORS

Up till now, the possible influence of psychological factors on CRT response has largely been neglected, with a paucity of studies having examined the role of psychological factors in health outcomes after CRT. A recent study showed that the personality trait negative affectivity (i.e., the tendency to experience increased negative emotions) exerted a stable adverse effect on perceived health status and disability, with patients scoring high on negative affectivity reporting poorer health status and more cardiac symptoms and disability over a 2-month period after CRT implantation.[57] However, the study did not control for the effect of echocardiographic and hemodynamic changes after CRT on health status. The interaction of traits, such as Type D personality (increased negative affectivity paired with social inhibition) may also influence the clinical CRT response, as this personality subtype has been associated with poorer quality of life and more symptoms and emotional distress in patients with CHF,[58] ischemic heart disease,[59] tachyarrhythmia's,[60,61] and peripheral artery disease.[62] In addition to personality traits, other psychological factors may be of importance in determining the clinical CRT response. For instance, several studies found that depression is common among patients with CHF and CAD, and is associated with an increase in cardiac morbidity and mortality and worse health status outcomes in these patients, independent of the underlying cardiac disease severity.[63-66] The American Heart Association advocates screening heart patients for depression to identify those who may require further assessment and treatment,[67] but more research is needed to investigate if this would improve depressive symptoms and cardiac outcomes in these patients.[68] Also, positive affect, coping style, loneliness, and marital quality may have notable effects on health outcomes in CHF patients receiving CRT,[69-71] and may explain why some patients do not report better health status despite echocardiographic and hemodynamic improvements.

CONCLUSIONS AND RECOMMENDATIONS

The majority of established indicators of CRT response, including NYHA class and echocardiographic and hemodynamic parameters, are poor associates of patient reported symptoms and quality of life. As these indicators largely determine clinicians' care, and quality of life is very important from the patient's perspective,

current treatment of CHF might fail to satisfy patients' needs.[35] Moreover, it might be debatable whether a patient who does not report a better health status, despite improvements in established parameters of CRT response, is a true responder. Hence, we would recommend that patient-reported outcomes, such as health status, be assessed in standard clinical practice, in addition to objective measures of CRT response, in order to enhance risk stratification in CRT patients and to identify patients who may not benefit optimally from this treatment. With routine assessment of health status with a disease-specific questionnaire, patients whose health status does not improve after CRT can be identified and additional treatment options (e.g., changes in medication or psychological support) be considered. The incorporation of health status as a performance measure of high quality care has also been recommended by the American College of Cardiology, the American Heart Association, and the American Medical Association.[72]

As emphasized in a report from the National Heart, Lung and Blood Institute in the US,[73] studies are warranted that examine the determinants of patients' perception of symptoms and quality of life, including the potential moderating role of psychological factors, in particular personality traits. Knowing which factors are associated with negative patient reported health outcomes may provide targets for secondary intervention, thereby improving the clinical CRT response. In turn, this may even result in reduced morbidity and mortality after CRT, as patient reported health status provides additional information to indicators of CHF severity in predicting prognosis.[44] An overview of our recommendations is provided in Table 2.

Table 2. Recommendations for the expansion of criteria for response to CRT

1) Incorporate measures of health status in standard clinical practice
• Expand beyond physical aspects of health status in CHF patients
• Use disease-specific health status questionnaires, for example, the Minnesota Living with Heart Failure questionnaire (21 items)[74] or the Kansas City Cardiomyopathy Questionnaire (23 items)[75]
• Use serial assessments of health status and attend to those patients whose health status does not improve or further deteriorates after CRT
2) Include psychological factors as possible determinants of health status in CRT studies
• Assess the impact of personality traits, including Type D personality (Type D Scale-14),[76] and other psychological factors, such as depression, on health status
• Examine whether psychological factors moderate the effect of echocardiographic and hemodynamic changes after CRT on health status

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Appendix I. Clinical trials on cardiac resynchronization therapy

Clinical Trial	Design, Follow up	N	Inclusion criteria	Clinical Endpoints	Functional Endpoints	Echocardiographic Endpoints	Hemodynamic Endpoints	Neuro-hormonal Endpoints
MUSTIC SR[a] 2001[19]	Crossover CRT ON/OFF Single blind 6 months	67	NYHA III LVEF <35% LVEDD >60mm QRS >150ms	MLHFQ -13.6 points*** Patient preference: 85% preferred CRT ON Hospitalizations: 3 vs. 9*	VO_2max +1.2 ml/kg/min** **6MWD +73.5 m***			
MIRACLE[b] 2002[6]	Parallel arms CRT ON/OFF Double blind 6 months	453	NYHA III-IV LVEF ≤35% LVEDD ≥55mm QRS ≥130ms 6MWD ≤450m	**NYHA** 68% vs. 38% ≥-1 class*** **MLHFQ** -18 vs. -9 pnts** Clinical composite score: 67% vs. 39% improved*** Death or worsening HF requiring treatment: 16% vs. 24%*	VO_2max +1.1 vs. +0.2 ml/kg/min** **6MWD** +39 vs.+10 m** Exercise time +81 vs.+19 sec**	LVEF +4.6% vs.-0.2%*** LVEDD -3.5 vs. 0 mm*** MR area -2.7 vs.-0.5 cm^2*** QRS duration -20 vs. 0 ms***		
PATH-CHF[c] 2002[20]	Crossover CRT ON/OFF Double blind 12 months	41	NYHA III-IV sinus rhythm ≥55bpm QRS ≥120ms PR ≥150ms	NYHA 72% to class I-II††† MLHFQ -28.6 points††† Hospitalization: -45%†††	**VO_2max** +3.1 ml/kg/min††† **VO_2maxAT** +1.5 ml/kg/min† **6MWD** +89 m†††			
PATH-CHF II[a] 2003[21]	Crossover CRT ON/OFF Single blind 3 months	89	NYHA ≥II LVEF ≤30% QRS >120ms VO_2max <18ml/kg/min	NYHA -0.25 class*** MLHFQ -4.7 points*	**VO_2max** +1.37 ml/kg/min*** **VO_2maxAT** +0.87 ml/kg/min*** **6MWD** +26 m*			

COMPANION[c] 2004[11]	Parallel arms CRT vs. OMT Single blind 12 months	1520	NYHA III-IV LVEF ≤35% QRS ≥120ms PR ≥150ms	NYHA symptoms 61% vs. 38% improvement*** MLHFQ -25 vs. -12 points*** **All-cause mortality and hospitalization**: 56% vs. 68%* CV death or hospitalization: 45% vs. 60%** HF death or hospitalization: 31% vs. 45%**	6MWD +40 vs.+1 m***		SBP +2 vs. -4 mmHg** DBP 0 vs. 0 mmHg, ns	
CARE-HF[a] 2005[22]	Parallel arms CRT vs. OMT Single blind 29.4 months	813	NYHA III-IV LVEF ≤35% LVEDD ≥30mm QRS ≥150 or ≥120ms with dyssynchrony	NYHA +0.6 class*** MLHFQ -10 points*** EQ-5D -0.08 points*** **All cause mortality or CV hospitalization**: 39% vs. 55%*** **Unplanned CV hospitalization**: 31% vs. 46%*** All cause death: 20% vs. 30%** Hospitalizations for worsening HF: 18% vs. 33%***		LVEF +6.9%*** LVEDD index -26.0 ml/m²*** MR area -0.04 cm²** Intraventricular mechanical delay -21 msec***	SBP +6.3 mmHg*** DBP +1.3 mmHg, ns HR +1 bpm, ns	NT pro-BNP -1122 pg/ml**

CRT *versus* ICD								
Clinical Trial	**Design, Follow up**	**N**	**Inclusion criteria**	**Clinical Endpoints**	**Functional Endpoints**	**Echocardiographic Endpoints**	**Hemodynamic Endpoints**	**Neuro-hormonal Endpoints**
CONTAK-CD[c] 2003[23]	Parallel arms CRT vs. ICD Double blind 6 months	501	NYHA ≥II LVEF ≤35%, QRS ≥120ms	NYHA 36% vs. 32% improved, ns MLHFQ -7 vs.+5 pnts, ns **All cause mortality, HF hospitalization or VT**: -15%, ns	VO_2max +0.8 vs. 0 ml/kg/min* 6MWD +35 vs.+15 m*	LVEF +5.1% vs.+2.8%* LVEDD -3.4 vs.-0.3 mm*** LVESD -4.0 vs.-0.7 mm***		
MIRACLE ICD[b] 2003[24]	Parallel arms CRT vs. ICD Double blind 6 months	369	NYHA III-IV LVEF ≤35% LVEDD ≥55mm QRS ≥130ms	**NYHA** -1 vs. 0 class** **MLHFQ** -17.5 vs.-11 points* Clinical status improved: 52.4% vs. 42.9%* Death or HF hospitalization: 25.7% vs. 25.9%, ns Death or all cause hospitalization: 47.4% vs. 48.3%, ns	VO_2max +1.1 vs. +0.1 ml/kg/min* **6MWD** +55 vs.+53 m, ns Exercise time +56 vs.-11 sec***	LVEF +2.1% vs.+1.7%, ns LVEDD -0.1 vs.-0.2 mm, ns LVESD -0.1 vs.-0.3 mm, ns LVEDV -19.9 vs.-5.7 ml, ns LVESV -22.2 vs.-8.2 ml, ns MR area -0.55 vs.-0.33 mm, ns QRS duration -20 vs.0 ms***		BNP -50 vs. -68 pg/ml, ns Dopamine 0 vs. 0 pg/mL, ns NE 4 vs. -17 ng/dL, ns Epinephrine 0 vs. -3 pg/mL* bET -2.5 vs. -1.8 pg/mL, ns

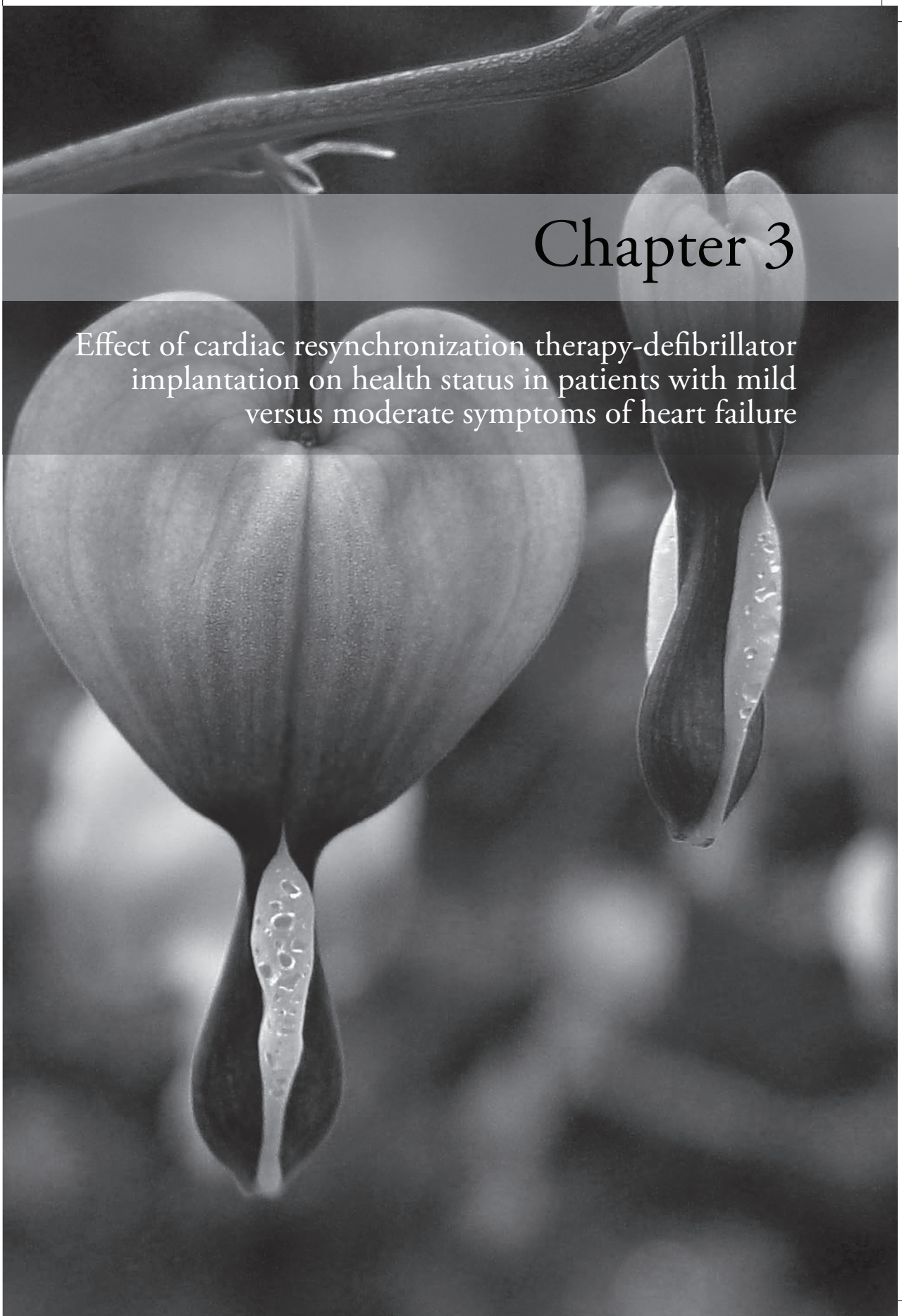
RHYTHM ICD[c] 2004[25]	Randomized ICD+CRT ON vs. ICD+CRT OFF Double blind 6 months	179	NYHA III-IV LVEF ≤35% QRS ≥150ms	NYHA -0.48 vs.-0.28 class* MLHFQ -7.8 vs.+3.4 points**	**VO_2max** +0.52 vs. -1.41 ml/kg/min*** 6MWD +13 vs.-15 m* Exercise time +58 vs.-50 sec**

Primary endpoints in bold print

[a] Results are presented as difference in means between CRT ON and CRT OFF/OMT
[b] Results are presented as difference in medians between baseline and follow-up for CRT ON vs. CRT OFF/ICD
[c] Results are presented as difference in means between baseline and follow-up for CRT ON (vs. OMT/ICD)

*$p \leq .05$ **$p \leq .01$ ***$p \leq .001$ for CRT ON vs. CRT OFF/OMT/ICD
†$p \leq .05$ ††$p \leq .01$ †††$p \leq .001$ for baseline vs. follow-up

6MWD=6-minute walking distance; bET=big endothelin; BNP=brain natriuretic peptide; CARE-HF=Cardiac Resynchronization-Heart Failure; CONTAK-CD=CONTAK-Cardiac Defibrillator; COMPANION=Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT=cardiac resynchronization therapy; CV=cardiovascular; DBP=diastolic blood pressure; EQ-5D=EuroQol-5D; HF=heart failure; LVEDD=left ventricular end-diastolic diameter; ICD=implantable cardioverter defibrillator; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESD=left ventricular end-systolic diameter; LVESV=left ventricular end-systolic volume; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD=Multicenter InSync ICD Randomized Clinical Evaluation; MLHFQ=Minnesota Living with Heart Failure Questionnaire; MR=mitral regurgitation; MUSTIC SR=Multisite Stimulation in Cardiomyopathies Sinus Rhythm; NT pro-BNP=N-terminal pro-brain natriuretic peptide; NYHA=New York Heart Association; OMT=optimal medical treatment; PATH-CHF=Pacing Therapies in Congestive Heart Failure; RHYTHM ICD=Resynchronization for Hemodynamic Treatment for Heart Failure Management; SBP=systolic blood pressure; VO_2max=oxygen uptake at peak exercise; VO_2max AT=oxygen uptake at anaerobic threshold.



Chapter 3

Effect of cardiac resynchronization therapy-defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure

ABSTRACT

Background Indications for cardiac resynchronization therapy (CRT) have expanded to include patients with mild congestive heart failure (CHF) symptoms (New York Heart Association (NYHA) functional class II) because of a demonstrated morbidity reduction in this subset of patients. However, little is known about post implantation changes in their self-reported health status compared to patients with more severe CHF. The aim of this study was to examine the influence of baseline NYHA functional class on health status changes in the first 12 months after implantation of an CRT-defibrillator (CRT-D).

Methods Patients with a first-time CRT-D (*N*=169, 75% men, mean age=62.1±10.7 years) were recruited from 3 Dutch hospitals. All patients completed the Short Form Health Survey 36 (SF-36) at the time of implantation and at 12 months after implantation.

Results Both mildly (NYHA functional class II, *n*=54) and moderately (NYHA functional class III, *n*=115) symptomatic CHF patients showed improved health status in several SF-36 domains at 12 months after CRT-D implantation. When adjusting for baseline health status, the groups did not differ with respect to their health status improvement over time, but after adjustment for demographic and clinical factors, the mildly symptomatic patients reported relatively more improvement in General Health (B=10.15, SE=3.31, *p*=.003) and Social Functioning (B=10.64, SE=3.74, *p*=.005).

Conclusions NYHA functional class II patients reported equal, and in some domains even more improvement in health status compared to NYHA functional class III patients at 12 months post CRT-D implantation. Hence, CRT not only prevents clinical adverse events in patients with mild CHF symptoms but also improves health status.

Versteeg H, van den Broek KC, Theuns DAMJ, Mommersteeg PMC, Alings M, van der Voort PH, Jordaens L, Pedersen SS. Effect of cardiac resynchronization therapy-defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure. Am J Card, *in press*.

INTRODUCTION

Besides reducing mortality and morbidity, another important target of treatment in congestive heart failure (CHF) patients is relief of symptoms as well as improvement in health status and quality of life.[1] Several trials have shown that cardiac resynchronization therapy (CRT), often in combination with an implantable cardioverter defibrillator (ICD) leads to improved patient reported outcomes in patients with moderate to severe (New York Heart Assocation (NYHA) functional class III or IV) CHF symptoms,[2-5] but the few available studies on patients with mild (NYHA functional class I or II) CHF symptoms did not demonstrate any health status benefits of CRT with ICD (CRT-D) implantation.[5,6] An explanation could be that mildly symptomatic patients have less room for improvement or that the follow-up time should be longer than the 6 months used in the latter studies in order to be able to demonstrate a benefit.[7] No study so far has directly compared the health status improvements reported by mildly and moderately symptomatic CHF patients after CRT-D implantation.

Hence, the objective of this multicenter prospective study was to examine changes in several health status domains in the first 12 months after CRT-D implantation in patients with mild (NYHA functional class II) *versus* moderate (NYHA functional class III) CHF symptoms.

METHODS

Patients receiving a first-time CRT-D implantation between May 2003 and September 2009 at the Erasmus Medical Center, Rotterdam, the Catharina Hospital, Eindhoven, and the Amphia Hospital, Breda, the Netherlands, and with NYHA functional class II or III CHF symptoms constituted the patient sample for the present study. Patients included in the Erasmus Medical Center participated in the ongoing Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria for all hospitals were significant cognitive impairments, a history of psychiatric illness other than affective/anxiety disorders, a life expectancy less than 1 year, NYHA functional class I or IV CHF symptoms, and insufficient knowledge of the Dutch language.

At baseline and at 12 month follow-up, patients were asked to complete a set of standardized and validated questionnaires. The study protocol was approved by the Medical Ethics Committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Demographic variables included sex, age, marital status (single *versus* having a partner), employment status (currently employed *versus* unemployed) and educational level (primary schooling or lower *versus* secondary schooling or higher), and were obtained via purpose-designed questions at baseline. Information on smoking and the use of psychotropic medications was also obtained through purpose-designed

questions at baseline. Information on other clinical variables, including cause of heart failure (ischemic *versus* non-ischemic), ICD indication (primary *versus* secondary prevention), NYHA functional class (II *versus* III), left ventricular ejection fraction (LVEF; ≤35% *versus* >35%), QRS duration (<150ms *versus* ≥150 ms), diabetes, and cardiac medications, were extracted from patients' medical records. Information on the occurrence of shocks (appropriate and inappropriate) during follow-up was obtained by means of device interrogation.

The Short Form Health Survey 36 (SF-36) was used to assess health status.[8] The SF-36 comprises 36 items, divided into 8 subscales: Physical Functioning, Role Physical Functioning, Bodily Pain, General Health, Social Functioning, Role Emotional Functioning, Mental Health, and Vitality. Scores on the subscales are linearly converted into a score between 0 and 100. A higher score on the SF-36 domains represents better functioning; a high score on the Bodily Pain domain indicates absence of pain. The Dutch version of the SF-36 has been validated in several Dutch populations and has a good internal consistency with a mean Cronbach's alpha of .84 across all scales.[9] Patients were asked to complete the SF-36 at baseline and at 12 months after implantation.

Discrete variables were compared using Chi-square tests and continuous variables (e.g. the baseline health status scores) using Student's *t* tests for independent samples. Paired-samples *t* tests were used to evaluate intragroup changes in health status scores from baseline to 12 months. To compare the NYHA functional class II and III patients with respect to change in health status in the first 12 months after CRT-D implantation, analyses of covariance (ANCOVAs) were performed, with the absolute change in health status (12-month score minus baseline score) as the outcome variable and baseline health status scores as covariate. Because we expected the health status scores of NYHA functional class II and III patients to differ at time of implantation, we included baseline health status score as a covariate to correct for the phenomenon of regression to the mean.[10] Finally, a set of demographic and clinical variables were included as covariates to adjust for potential confounding. A priori, on the basis of published research, we decided to include age, sex, ICD indication, cause of heart failure, LVEF, QRS duration, diabetes, psychotropic medications, and ICD shocks. All tests were two-tailed, and *p*-values of ≤.05 were considered to indicate statistical significance. A Bonferroni correction was applied to adjust for multiple comparisons ($p \leq .006$ ($p = .05/8$)). All analyses were performed with SPSS 17.0 for Windows (SPPS Inc., Chicago, Illinois).

RESULTS

Information on NYHA functional class was not reported in the medical records for 25 of the 261 patients willing to participate. Of the remaining 236 patients, 14 did not complete the SF-36 at baseline and 53 patients did not complete the SF-36 at follow-

up. The 169 patients eligible for analysis (72%) were on average less likely to have diabetes mellitus (14% *versus* 27%, p=.01) and to have ischemic causes of heart failure (50% *versus* 69%, p=.003), but more likely to use angiotensin-coverting enzyme (ACE)-inhibitors (82% *versus* 71%, p=.03) compared to excluded patients (n=92). No other systematic differences were found between participants and nonparticipants on baseline characteristics.

Table 1.Baseline characteristics for the total sample and stratified by mildly (NYHA II) *versus* moderately (NYHA III) symptomatic CHF

	Total (N=169)	NYHA II (n=54)	NYHA III (n=115)	p
Demographics				
Age, mean (SD)	62.1 (10.7)	61.5 (13.1)	62.5 (9.5)	.60
Women	42 (24.9)	11 (20.4)	31 (27.0)	.36
Lower education[a]	36 (21.3)	9 (16.7)	27 (23.4)	.29
Currently employed	37 (21.9)	12 (22.2)	25 (21.7)	.97
Having a partner	147 (87.6)	46 (85.2)	101 (87.8)	.53
Clinical factors				
Primary prevention	96 (56.8)	17 (31.5)	56 (48.7)	.04*
Ischemic etiology	84 (49.7)	26 (48.1)	58 (50.4)	.78
LVEF ≤35%	157 (92.9)	51 (94.4)	106 (92.2)	.31
QRS ≥150 ms	115 (68.5)	32 (59.3)	83 (72.8)	.08
Diabetes mellitus	23 (13.6)	5 (9.3)	18 (15.7)	.26
Shock(s) during follow-up	17 (10.1)	5 (9.3)	12 (10.4)	.81
Smoking	19 (11.2)	8 (14.8)	11 (9.6)	.32
Medication				
Amiodarone	34 (20.1)	14 (25.9)	20 (17.4)	.20
Beta-blockers	144 (85.2)	45 (83.3)	99 (86.1)	.64
Digoxin	40 (23.7)	10 (18.5)	30 (26.1)	.28
Statins	101 (59.8)	28 (51.9)	73 (63.5)	.15
ACE-inhibitors	139 (82.2)	42 (77.8)	97 (84.3)	.30
Diuretics	137 (81.1)	38 (70.4)	99 (86.1)	.02*
Psychotropic medication	29 (17.2)	10 (18.5)	19 (16.5)	.73

Results are presented as n (%), unless otherwise stated.
*p≤.05
[a] Less than secondary school
ACE=angiotensin converting enzyme; NYHA=New York Heart Association functional class; LVEF=left ventricular ejection fraction

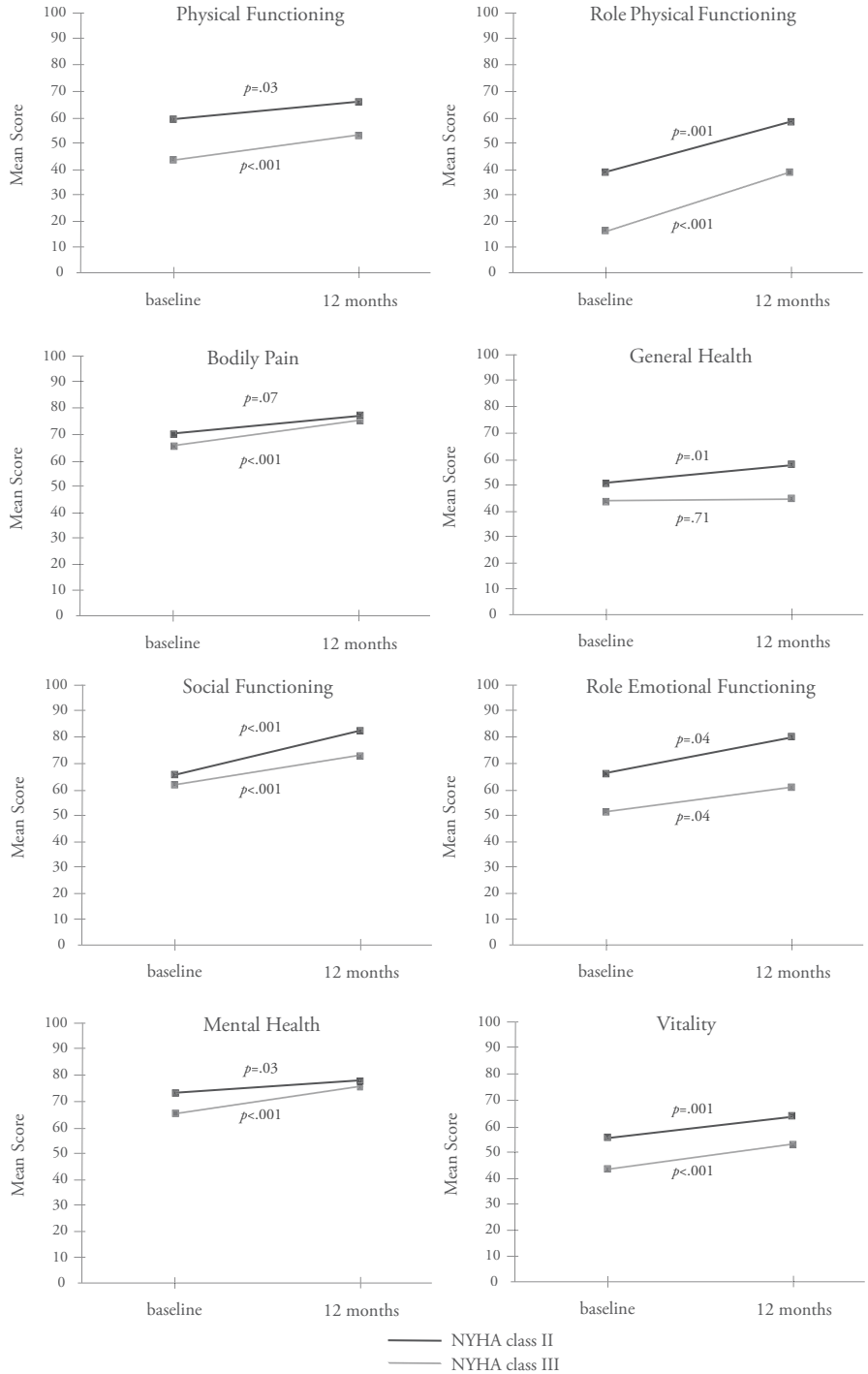
Baseline characteristics of the total patient sample and stratified by mild CHF symptoms (NYHA functional class II) versus moderate CHF symptoms (NYHA functional class III) are listed in Table 1. Of the 169 patients, 54 (32%) had mild CHF symptoms at the time of implantation. These patients were more likely to have ICDs for secondary prevention and less likely to use diuretics compared to patients with moderate CHF symptoms. No other statistically significant differences were found between mildly and moderately symptomatic patients on baseline characteristics.

At baseline, NYHA functional class II patients reported significantly better health status across 3 of 8 domains compared to NYHA functional class III patients: Physical Functioning (M=59.02, SE=3.03 *versus* M=43.73, SE=2.21, t_{167}=3.98, p<.001), Role Physical Functioning (M=38.43, SE=5.64 *versus* M=16.30, SE=2.76, $t_{79.4}$=3.52, p=.001), and Vitality (M=55.25, SE=2.47 *versus* M=43.42, SE=1.86, t_{167}=3.69, p<.001). Changes in health status scores across the domains of the SF-36 from baseline to 12- month follow-up are shown in Figure 1. Paired samples *t* tests showed that the NYHA functional class II patients significantly improved across 3 of 8 health status domains: Role Physical Functioning (M_{diff}=19.91, SE=5.81, t_{53}=3.42, p=.001), Social Functioning (M_{diff}=16.90, SE=3.19, t_{53}=5.30, p<.001), and Vitality (M_{diff}=8.89, SE=2.45, t_{53}=3.63, p=.001). The NYHA functional class III patients improved in 6 of 8 health status domains, except for Role Emotional Functioning (M_{diff}=9.57, SE=4.54, t_{114}=2.11, p=.04) and General Health (M_{diff}=0.72, SE=1.97, t_{114}=0.37, p=.71).

To correct for the phenomenon of regression to the mean we performed ANCOVAs including baseline health status as a covariate. Given an equal (or averaged) score at baseline, the NYHA functional class II and III patients did not significantly differ with respect to their change in health status from baseline to 12 months after implantation (Table 2). However, when adjusted for demographic and clinical factors, NYHA functional class II patients scored on average 10.15 points higher on General Health (SE=3.31, p=.003) and 10.64 points higher on Social Functioning (SE=3.74, p=.005) at 12 months after implantation compared to the NYHA functional class III patients.

With respect to the demographic and clinical factors, the use of psychotropic medication was associated with significantly less improvement (range B's=-10.59 to -16.45, all ps≤.006), while prolonged QRS duration (≥150 ms) was associated with more improvement (range B's=10.99 to 19.67, all ps≤.006) in 3 of 8 health status domains. Of note, ICD shocks during follow-up were not associated with change in health status domain scores.

Figure 1. Changes in health status scores of mildly (NYHA II) *versus* moderately (NYHA III) symptomatic CHF patients



Reported *p*-values represent the significance levels of the intragroup changes in health status

Table 2. Influence of baseline NYHA functional class (II *versus* III) on change in health status over time

Health status domain	B[a] (SE)	95% CI	*p*
Physical Functioning	3.90 (3.77)	-3.54-11.33	.30
Role Physical Functioning	9.74 (6.81)	-3.70-23.18	.15
Bodily Pain	-0.06 (3.77)	-7.51-7.38	.99
General Health	8.58 (3.26)	2.14-15.03	.01
Social Functioning	8.13 (3.61)	1.01-15.25	.03
Role Emotional Functioning	14.23 (6.40)	1.59-26.87	.03
Mental Health	-1.53 (2.70)	-6.86-3.81	.57
Vitality	3.85 (2.92)	-1.91-9.61	.19

Results of the ANCOVAs, adjusted for baseline health status

[a] A positive B-value indicates more improvement in health status of the NYHA II group compared to the NYHA III group; a negative B-value indicates less improvement in health status of the NYHA II group compared to the NYHA III group, given equal baseline values.

NYHA=New York Heart Association functional class.

DISCUSSION

In the present multicenter prospective study, we compared changes in patient reported health status in the first 12 months after CRT-D implantation in patients with mild (NYHA functional class II) versus moderate (NYHA functional class III) CHF symptoms. Both patient groups showed improved health status in several domains. When adjusting for baseline health status, the changes in health status over time were similar for both groups. However, after adjustment for demographic and clinical factors, the mildly symptomatic patients reported relatively more improvement in general health and social functioning.

To our knowledge, this is the first study directly comparing mildly and moderately symptomatic CHF patients regarding changes in health status after CRT-D implantation. Our results corroborate those of earlier studies in patients with moderate CHF symptoms showing significant improvement in patient reported health status after CRT-D implantation.[2-5] However, we were also able to show health status benefits of CRT-D in mildly symptomatic patients, which has not been shown by previous studies.[5,6] These studies used a relatively short follow-up period of 6 months and reported an overall health status score only. The present results indicate that mildly symptomatic patients report improvements in several health status domains at 12 months after CRT-D implantation; in some domains even more than moderately symptomatic patients.

The present results are important in light of the recent expansion of the indications for CRT to include CHF patients in NYHA functional class II.[11] The Multicenter

Automatic Defibrillator Implantation Trial (MADIT)–CRT, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, and Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) have shown that CRT-D is beneficial in these patients.[12–14] The present study suggests that mildly symptomatic CHF patients might also benefit from CRT-D in terms of improved health status. Improved patient reported health status is not only an essential treatment goal in itself,[1] but is also important for secondary prevention, because impaired health status is associated with poor prognosis in CHF patients, independent of indicators of disease severity.[15] Further studies are needed to determine whether CRT-D leads to better long-term clinical outcomes and survival in patients with mild CHF symptoms and whether the health status benefits seen at 12 months are also present in the long-term.[11]

Besides NYHA functional class III symptoms, another clinical factor associated with less health status improvements in the first year after CRT-D was the use of psychotropic medication at time of implantation. Early identification and adjunctive treatment of patients with these risk factors might be useful in clinical practice. A factor that was associated with more health status improvement was a prolonged QRS duration (≥150 ms), which emphasizes that CRT-D is particularly effective in patients with significant inter-/intraventricular conduction delays. Previous studies, including REVERSE and MADIT-CRT, also showed that especially patients with a QRS duration ≥150 ms derived the greatest clinical benefit from CRT-D.[7,16] This should be investigated further, as QRS duration might be an essential factor in predicting response to CRT.

The limitations of the present study must be acknowledged. First, we did not control for CRT response or nonresponse, because we had no information on changes that may have occurred in NYHA classification, LVEF, and QRS duration during the follow-up period. Yet research has shown that changes in these parameters are only marginally associated with patient reported changes in CHF symptoms and quality of life.[17,18] Second, health status was assessed with a generic rather than a disease-specific measure, using a disease-specific measure generally being more sensitive to tap symptoms important to patients.[15] Third, the sample size of NYHA functional class II patients (n=54) was relatively small.

Despite these limitations, this study also had several strengths, including its prospective study design with a 12-month follow-up period and the inclusion of several domains of health status. Most previous studies on health status in CRT- D patients have reported overall scores of health status.[5,6,19] The results of the present study show that it is important to look at the dimensions of health status separately, because using an overall score of health status may mask differences between subgroups on different dimensions of health status.

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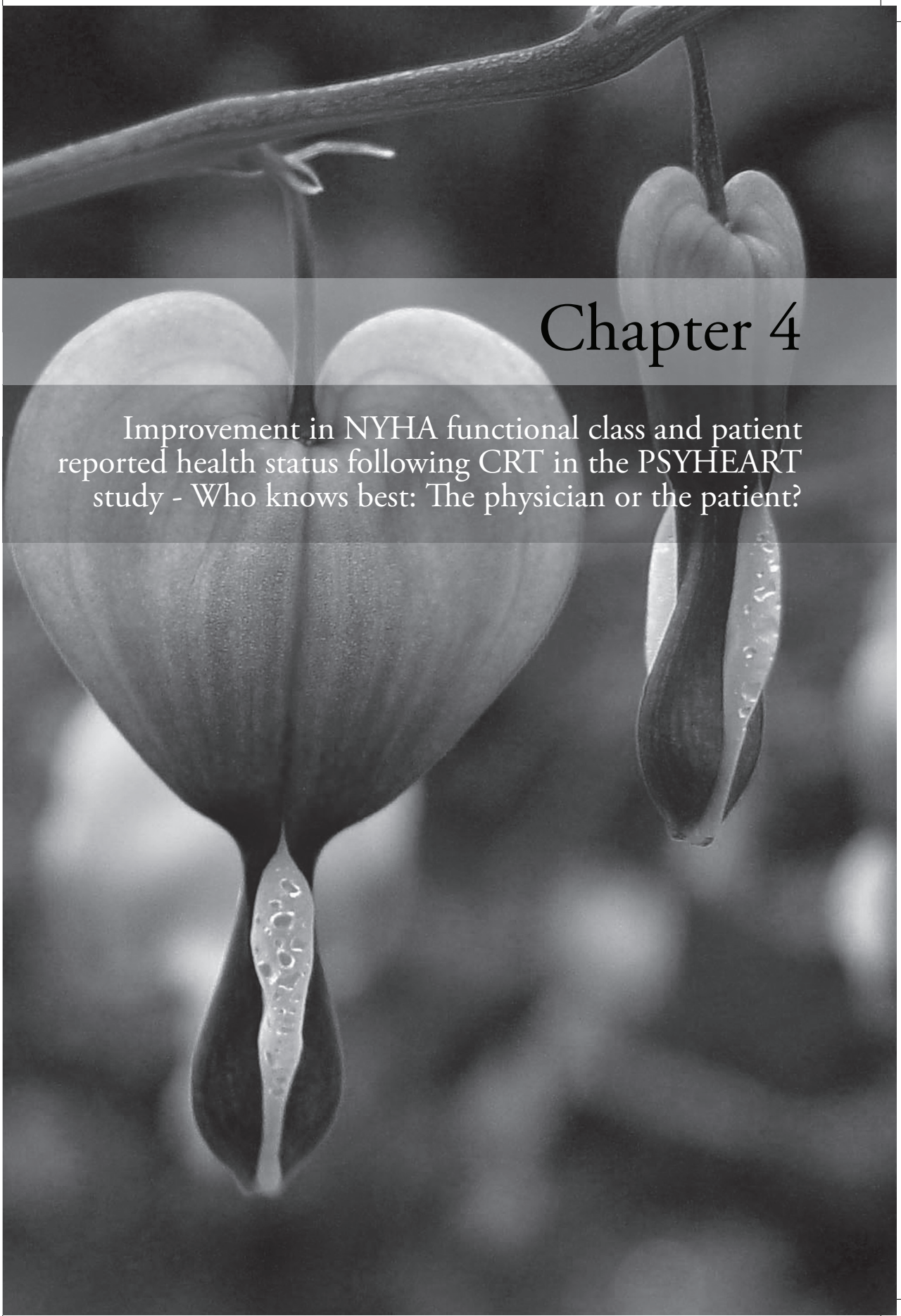

Chapter 4

Improvement in NYHA functional class and patient reported health status following CRT in the PSYHEART study - Who knows best: The physician or the patient?

ABSTRACT

Background A positive clinical response to cardiac resynchronization therapy (CRT) implies improvement in health status, including relief of symptoms, a decline in functional limitation, and improved quality of life. In cardiology practice, this is often defined as an improvement in NYHA functional class. We examined the association between improvement in physician rated NYHA functional class and patient reported health status in the first 2 months after CRT implantation.

Methods Consecutively implanted CRT patients (*N*=101, mean age=65.2±10.1, 28 women, NYHA: II (21), III (77), IV (3)) were recruited from the University Medical Center Utrecht, the Netherlands. All patients completed the Kansas City Cardiomyopathy Questionnaire (KCCQ) at the time of implantation and 2 months post implantation. Information on NYHA functional class was obtained from patients' medical records.

Results Of all patients, 42 (41.6%) improved by ≥1 NYHA class in the first 2 months after CRT implantation. Of the 59 patients whose NYHA functional class remained stable, 61% reported clinically relevant improvements in the KCCQ overall summary score, while only 45% of the patients reporting better health status also improved in NYHA functional class. Logistic regression results (*p*s≥.05) and c-statistics (range 0.53-0.61) confirmed that improvement in NYHA functional class was not associated with improvement in KCCQ scores.

Conclusions Our results show a large discrepancy between improvement in physician rated NYHA functional class and patient reported health status in the first 2 months after CRT implantation. This emphasizes that health status measures may have additional value over NYHA functional class in assessing short-term clinical response to CRT.

Versteeg H, Meine M, Tuinenburg AE, Doevendans PA, Denollet J, Pedersen SS. Improvement in NYHA functional class and patient reported health status following CRT in the PSYHEART study - Who knows best: The physician or the patient? *Submitted for publication.*

INTRODUCTION

Cardiac resynchronization therapy (CRT), often in combination with an implantable cardioverter defibrillator (ICD; CRT-D), is a promising treatment for a subset of patients with congestive heart failure (CHF).[1] CRT is recommended in patients who remain symptomatic (New York Heart Association (NYHA) functional class II-IV) despite optimal pharmacological therapy, with a depressed left ventricular ejection fraction (LVEF ≤35%), and an inter-/intraventricular conduction delay (QRS duration ≥120 ms, or ≥150 ms in NYHA functional class II patients).[2] Large-scale studies have demonstrated that the majority of these patients benefit from CRT,[3,4] but a significant proportion (10-40%) of patients does not respond to this treatment and are labeled nonresponders,[5,6] although no consensus exists regarding the definition of a positive response to CRT.[7]

As CHF is a debilitating chronic disease, a main goal of treatment is not only to prolong life, but also to relieve symptoms and to improve function and quality of life.[7,8] In clinical practice, this improvement in patient health status is most often defined as an improvement in ≥1 NYHA functional class. However, previous studies indicate that there is only a moderate association between physician rated NYHA functional class and patient reported health status, and most of the variation in health status scores cannot be explained by NYHA functional class alone.[9-11] These results suggest that clinically relevant changes in health status can occur in the absence of changes in NYHA functional class. Detecting changes in patient reported health status is not only essential to determine response to treatment as experienced by patients,[12] but also for secondary prevention as poor health status is an independent predictor of mortality and hospital readmission in CHF patients.[13,14]

The objective of the current study was to examine the association between improvement in physician rated NYHA functional class and patient reported health status in the first 2 months after CRT-implantation.

METHODS

Study design and participants

Patients receiving a first-time CRT(-D) implantation according to the current guidelines (NYHA functional class ≥II, LVEF ≤35 %, QRS ≥120 ms) in 2009 and 2010 at the University Medical Center Utrecht (UMCU), the Netherlands, comprised the patient sample for the current study. Patients participated in the ongoing 'The influence of PSYchological factors on health outcomes in HEART failure patients treated with Cardiac Resynchronization Therapy: A prospective, single-center, observational study (PSYHEART-CRT). The PSYHEART-CRT study was primarily designed to examine whether psychological factors moderate the effect of objectively assessed CRT response on patient reported outcomes in CHF patients. Exclusion criteria were age

<18 or >85 years, a history of psychiatric illness other than affective/anxiety disorders, cognitive impairments (e.g. dementia), on the waiting list for heart transplantation, and insufficient knowledge of the Dutch language. One day prior to implantation (baseline) and 2 months after implantation, patients were asked to complete a set of standardized and validated questionnaires. The study protocol was approved by the Medical Ethics Committee of the UMCU. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Measures

Demographic and clinical variables

Demographic variables included sex, age, marital status (single *versus* having a partner), employment status (currently employed *versus* unemployed), and educational level (primary school or lower *versus* secondary school or higher), and were obtained via purpose-designed questions at baseline. Information on clinical variables, including etiology (ischemic *versus* non-ischemic), ICD indication (primary *versus* secondary prevention), NYHA functional class (see text box below for classification criteria), LVEF, QRS duration, atrial fibrillation, diabetes, renal insufficiency (creatinine >120 umol/L), smoking, and cardiac and psychotropic medication, were extracted from the patients' medical records. For patients with a CRT-D device, information on the occurrence of shocks (appropriate and inappropriate) during follow-up was obtained by means of device interrogation.

Text box. New York Heart Association (NYHA) functional classification system[40]

NYHA functional class
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Disease-specific health status

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess disease-specific health status.[15] The KCCQ is a 23-item, self-report questionnaire that quantifies physical limitation, symptoms, social function, and quality of life of patients with CHF. These 4 health status subscales can be combined into a single overall summary score. Scores are transformed into a score from 0 to 100, with higher scores representing better functioning, fewer symptoms, and better quality of life. The validity and reliability of the KCCQ have previously been established and the measure was shown to be highly sensitive to clinical change in CHF patients over a 6-12 week period.[15-17] A mean difference over time of ≥5 points on the KCCQ overall summary score is considered a small, but clinically relevant change and has been associated with an 11% change in the adjusted hazard ratio of hospitalization and cardiovascular death.[13,17]

Statistical analyses

Discrete variables were compared with the Chi-square test and continuous variables with Student's *t* test for independent samples. The absolute changes in KCCQ health status scores were calculated (2 months minus baseline scores) and dichotomized into 'improved' *versus* 'not improved'. Regarding the KCCQ overall summary score, absolute changes of ≥5, ≥10, and ≥20 points were used to represent small, moderate, and large improvements, respectively.[17] Patients with stable and deteriorated KCCQ scores were combined because of limited sample size in the deterioration category; only 15 patients (14.9%) reported clinically relevant deteriorations in the KCCQ overall summary score (≥5 points) from baseline to 2 months.

Univariable and multivariable logistic regression analyses were performed to examine whether improvement in NYHA functional class was associated with improvements in KCCQ scores. A priori, we decided to include age, sex, etiology, baseline NYHA functional class, LVEF, QRS duration, AF, diabetes, renal insufficiency, and psychotropic medication in multivariable analyses. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) and c-statistics are reported. The c-statistic is equivalent to the area under the Receiver Operating Characteristic (ROC) curve and represents the ability of improvement in NYHA functional class to correctly discriminate patients who report clinically relevant improvement in KCCQ scores from those who do not. A c-statistic value of 0.50 indicates no discriminative ability, whereas a value of 1.00 indicates perfect discrimination.[18] All tests were two-tailed, and a Bonferroni correction was applied to adjust for multiple comparisons, with $p \leq .007$ ($p = .05/7$) indicating statistical significance. All analyses were performed with SPSS 17.0 for Windows (SPPS Inc., Chicago, Illinois).

Table 1. Baseline characteristics for the total sample, and stratified by (1) stable vs. improved NYHA class, and by (2) not improved vs. improved (≥5 points) KCCQ overall summary score

	Total	NYHA class not improved	NYHA class improved	*p*	KCCQ not improved	KCCQ improved	*p*
	(*N*=101)	(*n*=59)	(*n*=42)		(*n*=34)	(*n*=67)	
Demographics							
Age, mean (SD)	65.2 (10.1)	64.2 (10.7)	66.5 (9.2)	.28	65.6 (9.1)	64.9 (10.6)	.76
Women	28 (27.7)	17 (28.8)	11 (26.2)	.77	8 (23.5)	20 (29.9)	.50
Lower education[a]	13 (12.9)	7 (11.9)	6 (14.3)	.72	3 (8.8)	10 (14.9)	.54
Currently employed	22 (21.8)	13 (22.0)	9 (21.40	.94	11 (32.4)	11 (16.4)	.07
Having a partner	86 (85.1)	52 (88.1)	34 (81.0)	.32	30 (88.2)	56 (83.6)	.53
Clinical factors							
Primary prevention	80 (79.2)	45 (76.3)	35 (83.3)	.39	27 (79.4)	53 (79.1)	.97
Ischemic etiology	51 (50.5)	28 (47.5)	23 (54.8)	.47	19 (55.9)	35 (52.2)	.44
NYHA class III/IV	80 (79.2)	40 (67.8)	40 (95.2)	.001***	26 (76.5)	54 (80.6)	.63
LVEF(%), mean (SD)	23.6 (7.4)	24.9 (7.3)	21.7 (7.3)	.03*	23.4 (7.3)	23.6 (7.5)	.89
QRS(ms), mean (SD)	157.7 (25.4)	157.0 (26.3)	158.7 (24.3)	.74	154.7 (30.0)	159.3 (22.8)	.40
Atrial fibrillation	24 (23.8)	16 (27.1)	8 (19.0)	.35	9 (26.5)	15 (22.4)	.65
Diabetes mellitus	23 (22.8)	11 (18.6)	12 (28.6)	.24	7 (20.6)	16 (23.9)	.71
Renal insufficiency	35 (34.7)	19 (32.2)	16 (38.1)	.54	9 (26.5)	26 (38.8)	.22
Smoking	19 (18.8)	10 (16.9)	9 (21.4)	.57	5 (14.7)	14 (20.9)	.45
Medication							
Amiodarone	12 (11.9)	9 (15.3)	3 (7.1)	.20	7 (20.6)	5 (7.5)	.10
Beta-blockers	81 (80.2)	48 (81.4)	33 (78.6)	.73	26 (76.5)	55 (82.1)	.50
Digoxin	19 (18.8)	12 (20.3)	7 (16.2)	.64	7 (20.6)	12 (17.9)	.75
Statins	64 (63.4)	33 (55.9)	31 (73.8)	.07	21 (61.8)	43 (64.2)	.81
ACE-inhibitors	74 (73.3)	43 (72.9)	31 (73.8)	.92	24 (70.6)	50 (74.6)	.67
Diuretics	86 (85.1)	49 (83.1)	37 (88.1)	.48	31 (91.2)	55 (82.1)	.23
Psychotropic medication	24 (23.8)	16 (27.1)	8 (19.0)	.35	7 (20.6)	17 (25.4)	.59

Results are presented as *n* (%), unless otherwise stated.
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$
[a] Less than secondary school
ACE=angiotensin converting enzyme; NYHA=New York Heart Association functional class; LVEF=left ventricular ejection fraction.NYHA=New York Heart Association functional class.

RESULTS

Participants versus nonparticipants on baseline characteristics

138 consecutive CRT patients were asked to participate, of which 107 patients consented (response rate 77.5%). Six of these patients were not included in the analyses, as they did not complete the KCCQ (*n*=2) or their NYHA functional class was not reported (*n*=4) at follow-up. There were no systematic differences between participants (*N*=101) and nonparticipants (*n*=37) on baseline characteristics (results not shown).

Baseline characteristics of stable versus improved patients

Baseline characteristics of the total sample and stratified by (1) stable *versus* improved NYHA functional class and by (2) not improved *versus* improved KCCQ overall summary score (≥5 points), are shown in Table 1. Of all patients, 42 (41.6%) patients improved by ≥1 NYHA functional class in the first 2 months after CRT implantation (i.e., 2 patients improved by 2 classes, 40 patients improved by 1 class). These patients were more likely to be in NYHA functional class III or IV (95.2% *versus* 65.8%, $p<.001$; of note, only 3 patients were in NYHA functional class IV, they all improved to class III) and had a lower mean LVEF prior to implantation compared to the 59 patients whose NYHA functional class did not improve (21.7±7.3 *versus* 24.9±7.3, $p=.03$). There were no other systematic differences between these two patient groups on baseline characteristics. In total, 67 (66.3%) patients reported clinically relevant improvement in KCCQ overall summary score. These patients did not differ regarding baseline characteristics from patients reporting no KCCQ improvement.

Of note, one patient received an CRT-P and only 2 of the remaining 100 patients experienced appropriate ICD shock(s) during the follow-up period, one of them improved from NYHA functional class III to II, the other remained stable in NYHA functional class III. However, both reported no improvement in KCCQ overall summary score. None of the patients experienced inappropriate shocks.

Association between improvement in NYHA functional class and KCCQ scores

The patients with stable *versus* improved NYHA functional class did not differ in their baseline KCCQ subscale and overall summary scores (all *p*s>.05). Figure 1a shows the percentage of patients reporting improvement in KCCQ subscale scores stratified by stable *versus* improved NYHA functional class. Two thirds (59.3%-69.5%) of the 59 patients with stable NYHA functional class reported better functioning, less symptoms, or improved quality of life from baseline to 2 months post implantation. These proportions were lower than in the group of patients with improved NYHA functional class (70.7%-78.6%), but Chi-square tests showed that they were not significantly different (all *p*s>.007). Regarding the KCCQ overall summary score

(Figure 1b), 36 (61.0%), 33 (55.9%), and 23 (39.0%) of the patients with stable NYHA functional class reported small, moderate, and large improvements, respectively, *versus* 31 (73.8%), 27 (64.3%), and 20 (47.6%) of the 42 patients with improved NYHA functional class (p=.18, .40, and .39, respectively).

Figure 1a. Percentage of patients reporting improvements in KCCQ health status subscale scores, stratified by stable *versus* improved NYHA functional class

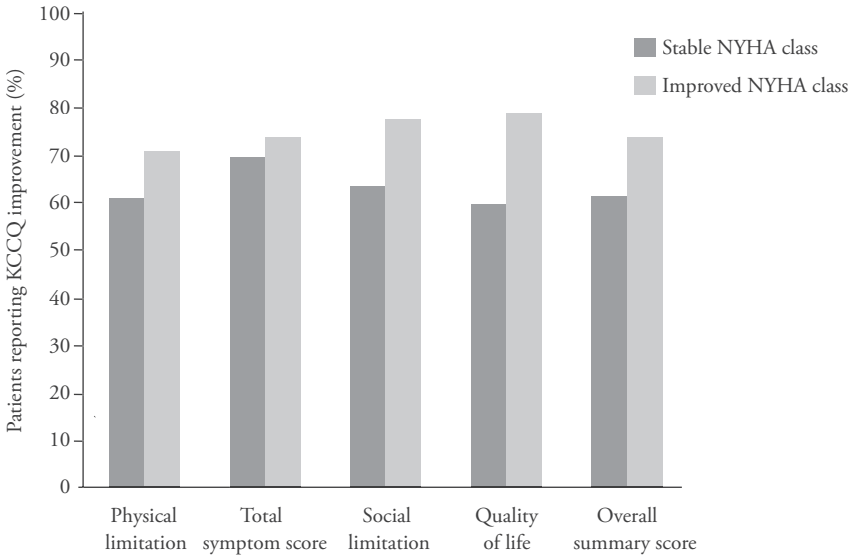

Figure 1b. Percentage of patients reporting small, moderate, and large improvements in KCCQ overall summary score, stratified by stable *versus* improved NYHA functional class

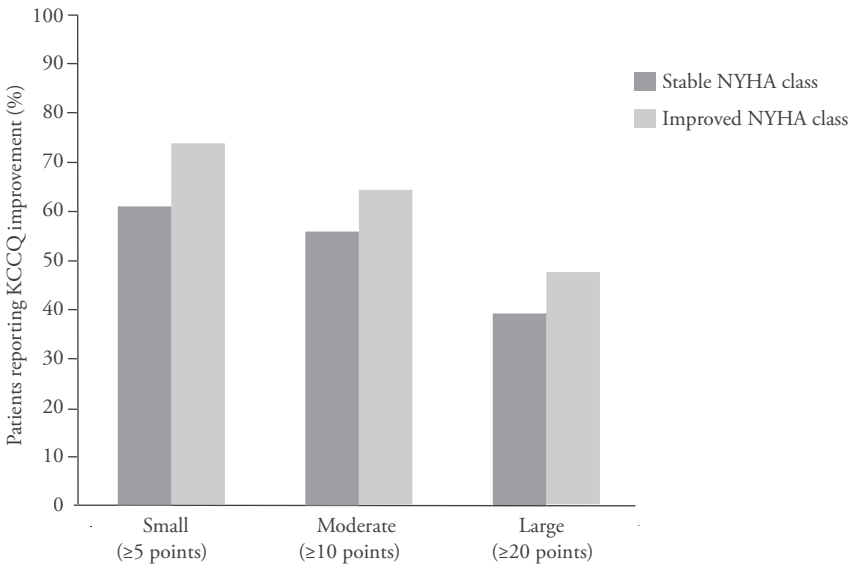

Table 2. Consistency between improvement in NYHA functional class and KCCQ scores

KCCQ improvement	Patients (%)/ NYHA class improved (%)[a]	OR [95% CI]	*p*	c-statistic
Physical limitation	63 (62.4) / 29 (46.0)	1.56 [0.66-3.70]	.31	0.55
Total symptom score	72 (71.3) / 31 (43.1)	1.24 [0.51-2.99]	.64	0.53
Social Limitation	64 (63.4) / 31 (48.4)	1.98 [0.78-5.04]	.15	0.58
Quality of life	68 (67.3) / 33 (48.5)	2.51 [1.02-6.20]	.05	0.61
Overall summary score, small (≥5 points)	67 (66.3) / 31 (46.3)	1.81 [0.76-4.27]	.18	0.57
Overall summary score, moderate (≥10 points)	60 (59.4) / 27 (45.0)	1.42 [0.63-3.20]	.40	0.54
Overall summary score, large (≥20 points)	43 (42.5) / 20 (46.7)	1.42 [0.64-3.17]	.39	0.54

[a] Percentage of the patients with KCCQ improvement

Table 2 represents the results of the logistic regression analyses showing that improvement in NYHA functional class was not associated with improvements in KCCQ (subscale) scores (all *p*s>.007). Accordingly, the c-statistics ranged from 0.53-0.61, indicating that improvement in NYHA functional class performs no better than chance in discriminating patients that experience improvements in KCCQ scores from those who do not. Improvement in NYHA functional class was most accurate, but still poor, in discriminating patients with improvements in the KCCQ quality of life score (c-statistic=0.61). When adjusting for age, sex, etiology, baseline NYHA functional class, LVEF, QRS duration, AF, diabetes, renal insufficiency, and psychotropic medication, the associations between improvement in NYHA functional class and KCCQ scores remained non-significant (range ORs=0.88-3.27, all *p*s>.007). Of note, none of the included covariates was significantly associated with improvement in KCCQ scores (all *p*s>.007).

DISCUSSION

In the current prospective study, we examined the association between improvement in physician rated NYHA functional class and patient reported health status in the first 2 months after CRT implantation. Results showed that in patients whose NYHA functional class remained stable, 60-70% did report improvements in health status (domain) scores. By contrast, only 45-47% of patients experiencing small to large improvements in overall health status also improved in NYHA functional class. Logistic regression results and c-statistics confirmed that improvement in NYHA functional class was not associated with improvement in KCCQ scores.

The current results emphasize previous findings that NYHA functional class should likely not be used as the sole measure reflecting changes in the severity of symptoms and functional limitations in CHF patients.[9-11] which is now often the case in clinical practice and research trials. The NYHA functional classification system has been criticized due to the method not being standardized[19,20] and due to poor interrater reliability.[20,21] The class that the physician decides to assign to a patient depends on the questions the physician asks and his/her interpretation of what comprises 'ordinary physical activity' and 'slight' versus 'marked' limitations.[20] In addition, criteria often used to determine NYHA functional class include 'self-reported walking distance' and 'difficulty in climbing stairs'.[20] These criteria, however, primarily assess general functional status and many factors may influence the patient's answer, including comorbidities, environmental and psychosocial factors, and perception of distance.[20,22,23] Serial assessment of patient reported health status using a disease-specific questionnaire offers physicians important additional information on how the patient is doing over time.[12,22] Also, it may optimize secondary prevention as health status measures have been shown to predict mortality and hospital readmissions in patients with CHF independent of traditional biomedical risk factors.[13,14]

Improvement in health status is particularly important from the patient perspective, as their primary concerns revolve around how a disease or treatment affects their daily lives,[8,24] Patient reported health status has been recommended as a performance measure of high quality care by the American College of Cardiology, the American Heart Association, and the American Medical Association,[25] and is increasingly seen as an important endpoint in clinical research.[26] Yet, the incorporation of health status measures in routine clinical practice is less common and more challenging due to a number of practical, methodological, and attitudinal barriers.[27,28] When these barriers are adequately addressed, the implementation of patient reported outcomes in clinical practice could have a number of potential benefits for both the physician and the patient.[27,29] It could enable physicians to detect and treat physical or psychological problems that otherwise might go unrecognized, promote the role of patients in clinical decision making, and enhance physician-patient communication, which in turn might improve patient satisfaction with care and adherence to treatment.[12,27,30] Preliminary evidence from oncology shows that incorporation of a health status measure in the clinical management of patients does not increase the time burden to physicians when they see patients for clinical consultations.[30]

The present study showed that neither improvement in NYHA class nor any of the baseline demographic and clinical factors included in adjusted analyses were associated with improvement in health status. These results are on a par with earlier studies showing a discrepancy between objective measures of disease severity and patient perceived symptoms and quality of life.[11,31,32] A growing body of evidence suggests that psychosocial factors (e.g. depressive and anxiety symptoms, personality traits)

have a notable impact on patient reported health status in CHF patients, irrespective of cardiac disease severity.[33-37] Studies are warranted that examine the demographic, clinical, and psychosocial determinants of patient health status after CHF treatment, which may help identify targets for secondary prevention.[38]

The limitations of the current study should be acknowledged. First, the follow-up period of 2 months might be too short to adequately assess response to CRT. In the first months after implantation, patient' health might be positively influenced by a placebo-effect, but also negatively by pain at the implantation site, limited arm and shoulder motion, and a driving restriction. However, our results show that clinically relevant changes in health status can occur within this short period of time. Second, our patient sample was relatively small and we had to combine patients with stable and deteriorated KCCQ scores into one group. Future studies with larger patient samples and longer follow-up periods are needed to confirm our results and to identify the determinants of health status changes after CRT implantation. Finally, for logistic reasons baseline assessment was done one day prior to implantation, which may have resulted in more impaired health status due to pre-implantation distress. However, the instruction of the KCCQ calls for the rating of symptoms, function, and quality of life in the past two weeks.

The present study also has several strengths. First, we used a disease-specific measure to assess health status, which was previously shown to be highly responsive to clinical change over a 6-week period.[16,17] We also examined proportions of patients who showed benefit instead of mean group changes. As previously mentioned, health status scores are influenced by demographic, clinical, and psychosocial factors, so there is a large variability in individual responses. Therefore, earlier studies on CRT response presenting mean changes in health status (i.e., the CRT group improved by 5 points more than the control group) could be misleading. For clinical practice, it is more relevant to focus on the proportion of patients achieving a particular benefit from treatment, be it a small, moderate, or large benefit, as this reflects changes in individual patients.[39]

To conclude, our results show a large discrepancy between improvement in physician rated NYHA functional class and patient reported health status in the first 2 months after CRT implantation. This emphasizes that health status scores may have additional value over NYHA functional class in assessing short-term clinical response to CRT. Hence, we would recommend the incorporation of health status measures in clinical practice to gain a better understanding of individual CHF patients' experiences and responses to treatment.

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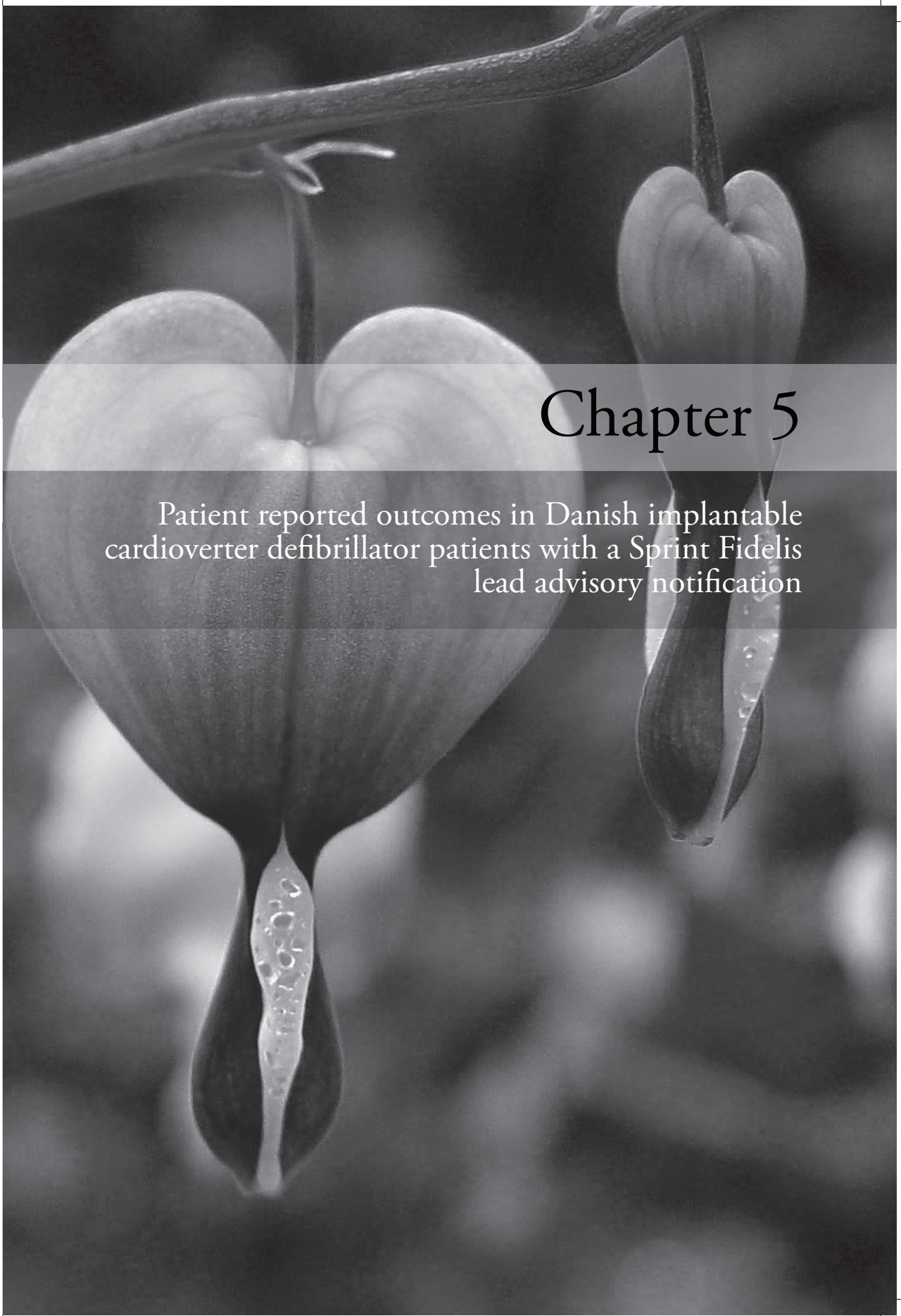


Chapter 5

Patient reported outcomes in Danish implantable cardioverter defibrillator patients with a Sprint Fidelis lead advisory notification

ABSTRACT

Background Few studies have investigated the association between implantable cardioverter defibrillator (ICD) and lead advisory notifications and patient reported outcomes (PROs). We examined (i) whether the mode used to inform patients about a device advisory is associated with PROs, and (ii) whether patients with a device advisory report poorer PROs compared to non advisory controls.

Methods Patients (n=207) implanted with an ICD at Aarhus University Hospital, Denmark, with a Sprint Fidelis lead subject to advisory and a non advisory control group (n=510) completed a set of standardized PRO measures. A Bonferroni correction was applied to all statistical PRO comparisons to adjust for multiple comparisons, with a p-value of .0038 (.05/13 PROs) indicating statistical significance.

Results Device advisory patients did not differ significantly on PROs according to mode of notification (all ps>.0038). They also did not differ significantly from controls on mean scores of depression, anxiety, device acceptance, and health status (all ps>.0038). Differences were only found on ICD concerns (p<.0001) and on the mental health status domain (p=.003), with advisory patients reporting fewer ICD concerns and a better mental health status than non advisory controls.

Conclusions The mode used to inform ICD patients about the advisory was not associated with PROs, nor was the overall well being of device advisory patients impaired compared to non-advisory controls. These results indicate that ICD patients are generally able to cope with a device advisory.

Pedersen SS, Versteeg H, Nielsen JC, Mortensen PT, Johansen JB. Patient reported outcomes in Danish implantable cardioverter defibrillator patients with a Sprint Fidelis lead advisory notification. Europace 2011; 13:1292-1298.

INTRODUCTION

Implantable cardioverter defibrillator (ICD) therapy is the first line treatment for the primary and secondary prevention of sudden cardiac death.[1] Despite its medical benefits, ICD therapy is associated with a potential for procedure-related (e.g., infection and bleeding) and device-related complications (e.g., inappropriate shocks and lead dysfunction).[2,3] Device-related complications, such as device dysfunction and lead fracture, have increased in the last decade, although it is not a new phenomenon.[4] However, guidelines are now in place from the Food and Drug Administration and the Heart Rhythm Society on device performance and also on how device advisory notifications should be communicated to patients.[5]

Device advisories may have an adverse influence on patient reported outcomes (PROs), such as well being and quality of life. As voiced in an editorial published in 2008 related to the Sprint Fidelis advisory, there is an urgent need to examine the influence of advisory notifications on patient well being both with respect to the impact of the advisory itself but also with respect to how to communicate the risk to patients.[6] A true estimation of the impact of advisories on patients may serve to counterbalance the associated negative publicity in the press, which has led to patients turning down this potentially life-saving treatment as reported in the United States.[7]

Few studies have examined the impact of device advisory notifications on patients, as assessed with PROs. In a recent viewpoint,[8] we identified 6 studies, with sample sizes ranging from 31-86 patients with hardware subject to a Class I or a Class II advisory.[9-14] The evidence for a psychological impact of device advisory notifications is mixed, as shown in an update of the literature, as presented in Table 1. Little is also known about the most appropriate way of communicating the risk associated with an advisory to patients and whether different modes may have a differential influence on PROs.[6]

In the current study, we examined (i) whether the mode used to inform patients about the Sprint Fidelis device advisory (i.e., informing patients by letter calling them in for an urgent clinical follow-up visit *versus* informing them ad-hoc during a routine clinical visit) is associated with mean scores on PROs, and (ii) whether patients with a device advisory notification report poorer PROs compared to non-advisory patients, assessed with both disease-specific and generic measures.

METHODS

Study design and participants

Patients (*n*=207, response rate 87%) implanted with an ICD between 1993 to 2009 at Aarhus University Hospital (Skejby), Denmark, and with a lead (6931 or 6949) subject to the Medtronic Sprint Fidelis ICD lead advisory, completed a set of standardized and validated PROs between September and October 2009. The Sprint

Table 1. Overview of studies on the impact of device advisories on patient reported outcomes

Authors	Origin of study	Advisory	N	Response rate	Study design	Time advisory assessment	Endpoint	Impact of device advisory
Birnie et al. (2009)[14]	Canada	Class II advisory (Medtronic)	86 advisory patients; 94 controls	Patients 70.5% Controls 70.1%	Case-control	>24 months	Device acceptance[b]	No significant impact
van den Broek et al. (2006)[9]	The Netherlands	Class II advisory (Medtronic)	33 advisory patients	90%	Prospective; 14 ± 4 months follow-up	<2 months*	Anxiety[a]	Increase in the number of anxious patients from 6.1% pre compared to 24.2% post advisory
Cuculi et al. (2006)[13]	Switzerland	Class I advisory (Guidant)	30 advisory patients; 25 controls	*Not reported*	Case-control	<1 month	Distress[a]	No significant impact; 3 distress measures were significantly higher in the controls
Gibson et al. (2008)[12]	USA	Class I advisory: 13/31 (42%) (Guidant)	31 advisory patients; 50 controls	89%	Case-control	<1 to >4 months	Distress[a]; QoL[a]	No significant impact
Heatherly et al. (2011)[36]	USA	Class I advisory (Medtronic)	158 advisory patients; 255 controls	*Not reported*	Case-control	14-22 months	ICD concerns[b]	More ICD concerns in recalled group – primarily due to shocks

Keren et al. (2011)[29]	Canada	Class II advisory (Medtronic)	24 advisory lead fracture; 249 advisory no fracture; 143 controls	92% advisory lead fracture; 74% advisory no fracture; 62% controls	Case-control	13 months	Anxiety[a,b]; depression[a]; device acceptance[b]	No difference in distress between no fracture and controls; more distress in advisory fracture patients due to inappropriate shocks
Sneed et al. (1994)[10]	USA	Class II advisory (Guidant)	31 advisory patients; 21 caregivers	100%	Prospective, case-control; 1-month follow-up	1 to 3 months	Distress[b]; uncertainty[b]; confidence in device[b]	Patient and caregiver confidence decreased; anxiety increased in patients and confusion in caregivers over time
Undavia et al. (2008)[11]	USA	Class I advisory: 43/61 (70%) (*not mentioned*)	61 advisory patients; 43 controls	90%	Case-control	7.6±1.6 months	Anxiety[a]; depression[a]; QoL[b]	No significant impact

Adapted from Pedersen et al[8]

[a] Generic measure

[b] Disease-specific measure

[*] conveyed via personal communication with the author

QoL=quality of life

Fidelis ICD lead advisory was issued due to potential lead fracture that could lead to unnecessary (inappropriate) shocks but also failure to deliver life-saving defibrillating shocks. Lead Integrity Alert™ (LIA; Medtronic, Mineapolos, MN, USA) software was made available for download to the device which would alert patients of potential lead failure. In Denmark, the Sprint Fidelis lead advisory was issued on October 15, 2007. All of our patients were informed about the LIA software and the rationale at the time of downloading it to their device.

Patients were informed about the advisory in one of the following two ways: (i) by letter in December of 2008, calling patients in for an urgent clinical follow-up visit, and (ii) ad-hoc during a routine clinical visit. Hence, for patients in group (i) the time interval between the device advisory notification and completing the questionnaires was 9 months, whereas for group (ii) the interval was variable. Both groups had the LIA software downloaded to their device during the clinical follow-up visit.

A control group of patients (*n*=510), implanted with an ICD between 1991 and 2006 at our institution but whose hardware was not under advisory, had completed the same questionnaires for a previous study (response rate 84%).[15,16] For the majority of the control patients (i.e., 95%), the main indication for ICD was secondary prevention, as primary prevention was not generally implemented in Denmark before 2007. Both advisory and control patients had to be ≥18 years of age to be eligible to participate. For both groups, if the questionnaire was not returned within 2 weeks, a reminder was sent by post including a duplicate questionnaire. The study was conducted according to the Declaration of Helsinki.

Measures

Demographic and clinical variables

Information on demographic and clinical variables was obtained from the Danish ICD Register[17] or from purpose-designed questions in the questionnaire.

Symptoms of anxiety and depression

We used the 14-item Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression.[18] Items are answered on a 4-point Likert scale from 0-3 (score range 0-21), with 7 items contributing to the anxiety and depression subscales, respectively. A high score on the HADS indicates more symptoms of anxiety and depression. A cut-off score ≥8 for both subscales represents probable clinical levels of anxiety and depression.[19] The HADS is a valid and reliable instrument that has been used across the world in cardiac and non-cardiac populations,[19] and that is not prone to confounding by symptoms of somatic disease.[20]

Device-related concerns

The Implantable Cardioverter Defibrillator Patient Concerns Questionnaire (ICDC)

is an 8-item self-report measure tapping into concerns about the ICD giving a shock (e.g., 'I am worried about my ICD firing').[21,22] Items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much so), with a higher score indicating a higher level of device-related concerns (score range 0-32). The internal consistency of the 8-item ICDC is good, with Cronbach's alpha=.91.[22] Previously, we have shown that high levels of pre implantation ICD concerns predict mortality in ICD patients.[23]

Device acceptance

Device acceptance was assessed with the 18-item Florida Patient Acceptance Survey (FPAS).[24] Items (e.g., 'When I think about the device, I avoid doing things that I enjoy' and 'I feel less attractive because of my device') are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree) Of all items, 15 contribute to a total score, while the remaining 3 items are filler items. A high score indicates better acceptance. The convergent, divergent, and discriminant validity of the FPAS are good, and the scale has been shown to be internally consistent, as indicated by Cronbach's alpha of .83 for the total scale. Previously, we have validated the FPAS in Danish ICD patients, with this specific language version indicating good validity and reliability.[25]

Health status

We used both a disease-specific and generic measure of health status. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a disease-specific measure, comprising 21 items.[26] Items are answered on a 6-point Likert scale from 0 (no) to 5 (very much). The total score ranges from 0 to 105, with a higher score indicating poor health status. The measure is psychometrically sound, with good internal consistency as measured by Cronbach's alpha=.91-.96 for the total scale.

The Short Form Health Survey (SF-36) is a generic measure of health status, comprising 36 items that contribute to 8 domains: Role Physical Functioning, Role Emotional Functioning, Physical Functioning, Mental Health, Vitality, Social Functioning, Bodily Pain, and General Health.[27,28] Scale scores range from 0 to 100, with a higher score indicating better functioning. The scale has good reliability with Cronbach's alpha ranging from .65 to .96 for all subscales.[27]

Statistical analyses

The three patient groups, that is (i) device advisory patients informed by letter urging them to come in for a clinical follow-up visit, (ii) device advisory patients informed ad-hoc during a clinical follow-up visit, and control patients without a device or leads subject to an advisory notification, were compared on baseline characteristics using analysis of variance (ANOVA) with a post-hoc Bonferroni correction (if applicable) for continuous variables and the Chi-square test for nominal variables. Student's *t* test for independent samples was used to compare the two device advisory groups

on PROs, and the device advisory group (irrespective of how information was given about the advisory) with the control group on PROs. Due to multiple comparisons that increase the chance of finding a statistically significant result and to prevent making a Type I error (also known as a false positive), we used a Bonferroni correction for these analyses. Accordingly, given that we had 13 PROs, we divided the standard *p*-value of .05 by 13, using a *p*-value of .0038 to indicate statistical significance for the interpretation of these results. However, for all results both in the text and in the figures the exact *p*-value for each comparison is also reported. All analyses were performed using SPSS 17.1 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Baseline characteristics stratified by advisory groups (i) and (ii) *versus* no advisory (control group) are displayed in Table 2. The groups did not differ systematically on baseline characteristics, except that advisory group (i) patients were more likely to have a defibrillator with cardiac synchronization therapy (CRT-D) device than advisory group (ii) patients and controls, and advisory group (ii) patients were more likely to be prescribed beta-blockers compared to advisory group (i) patients and controls. Time since first ICD implant was longer for controls compared to advisory group (i) and (ii) patients.

Patient reported outcomes in advisory patients stratified by mode of notification

No statistically significant differences were found on psychological distress (Figure 1a) and health status (Figure 1b) between group (i) patients who were notified about the device advisory by letter calling them in for an urgent clinical follow-up visit and group (ii) patients who were informed ad-hoc during a routine clinical follow-up visit, with all *p*s>.0038 which was chosen to indicate statistical significance.

Patient reported outcomes stratified by device advisory versus control patients

Given that we found no statistically significant differences on PROs between the two advisory groups stratified by mode of notification, we merged the groups (i) and (ii) and compared device advisory patients with a non-advisory control group to examine potential differences in PROs. There were no statistically significant differences between advisory and non-advisory patients on symptoms of depression and anxiety, while advisory patients reported less ICD concerns than non-advisory controls (5.12±6.04 vs. 7.67±8.28, $p<.0001$) (Figure 2a). As for device acceptance and disease-specific and generic health status, there was only one difference between groups, with advisory patients reporting better mental health status than non-advisory controls (82.46±17.73 vs. 77.90±19.10, $p=.003$) (Figure 2b).

Table 2. Baseline characteristics stratified by device advisory *versus* no advisory

	Device advisory (i) (*n*= 74)	Device advisory (ii) (*n* = 133)	Controls (*n* = 510)	*p*
Demographics				
Women	8 (10.8)	20 (15.0)	92 (18.0)	.26
Age, mean (SD)	63.2 (13.2)	61.6 (14.7)	64.0 (13.1)	.18
Partner/married	58 (78.4)	102 (77.1)	393 (77.5)	.94
Clinical Factors				
CRT-D	22 (30.1)	30 (22.6)	92 (18.0)	.04
Comorbidities	15 (20.8)	29 (22.3)	116 (23.0)	.92
Ischemic heart disease	49 (70.0)	81 (67.5)	327 (70.6)	.80
Smoking	13 (17.6)	26 (19.8)	119 (23.8)	.36
Time since first ICD implant (yrs), mean (SD)	2.0 (1.1)	2.2 (1.5)	5.3 (3.2)	<.001[a]
Medication				
Amiodarone	10 (15.4)	34 (27.0)	123 (24.4)	.19
Beta-blockers	54 (83.1)	116 (92.1)	412 (82.4)	.03
Diuretics	28 (43.1)	54 (42.9)	236 (46.9)	.64
Thiazide diuretics	10 (15.4)	12 (9.5)	46 (9.3)	.30
ACE-inhibitors	52 (80.0)	98 (77.8)	345 (69.8)	.07
ARBs	13 (20.0)	37 (29.4)	156 (31.1)	.18
Digoxin	15 (23.1)	23 (18.3)	84 (16.7)	.43
Psychotropic medication	11 (16.9)	9 (7.2)	67 (14.1)	.08

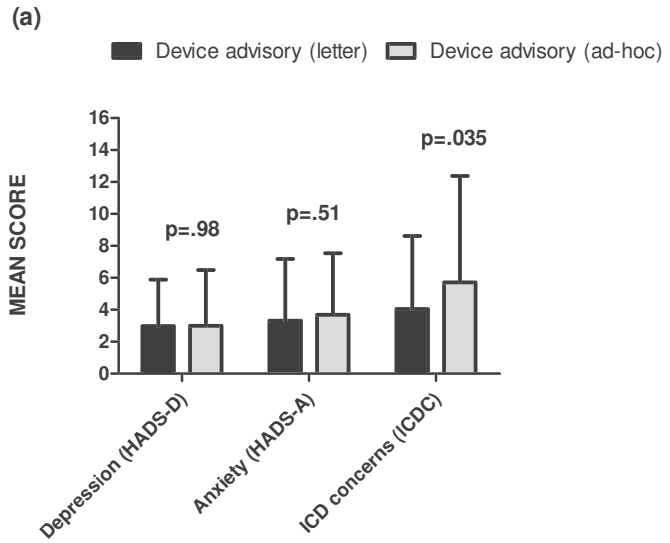
Results are presented as *n* (%) unless otherwise indicated.

(i) Notification of the device advisory by letter in December of 2008 calling patients in for an urgent clinical follow-up, and (ii) ad-hoc during a routine clinical visit.

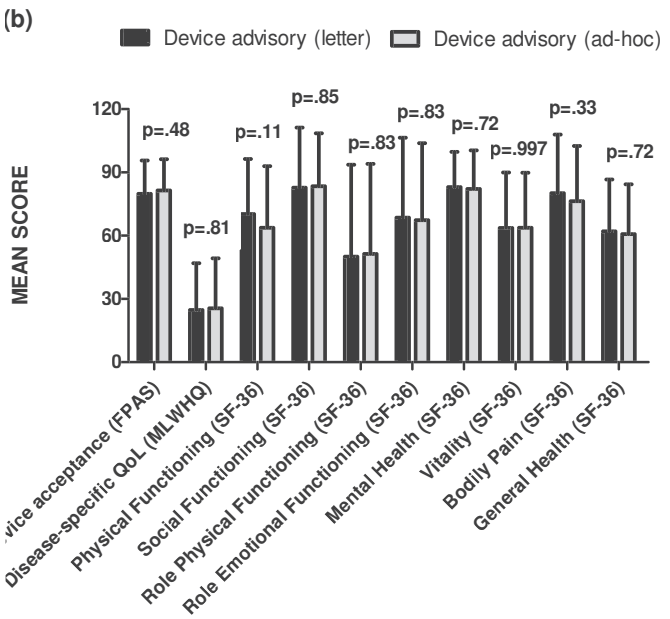
[a] Group differences were significant between controls and device advisory (i) patients and between controls and device advisory (ii) patients (post-hoc Bonferroni *p*s<.0001) but not between device advisory (i) and device advisory (ii) patients (post-hoc Bonferroni *p*=1.00)

ACE=angiotensin converting enzyme; ARB=Angiotensin II receptor antagonists; CRT-D=cardiac resynchronization therapy with defibrillation.

Figure 1. (a) Psychological distress and (b) health status stratified by device advisory notification mode

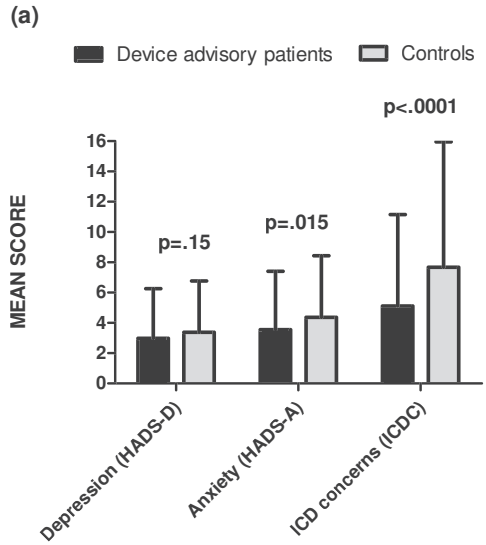


All comparisons were non significant with a Bonferroni correction (all ps > .0038)

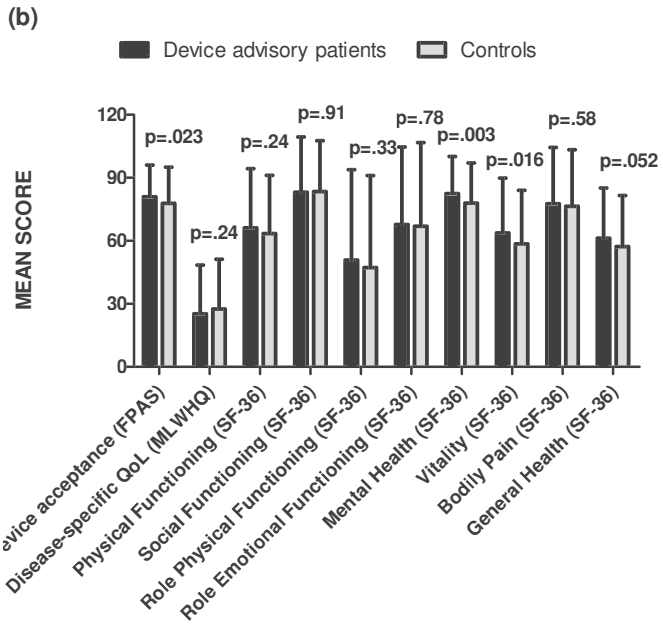


All comparisons were non significant with a Bonferroni correction (all ps > .0038)

Figure 2. (a) Psychological distress and (b) health status stratified by device advisory status



All comparisons were non significant with a Bonferroni correction (all ps > .0038), except for ICD concerns



All comparisons were non significant with a Bonferroni correction (all ps > .0038)

DISCUSSION

Device advisories may be unnerving to patients and may reduce patient confidence in their device. For this reason, it is important to examine the impact of device advisories on patient well being and device acceptance both with respect to the impact of the advisory itself but also with respect to how best to communicate the risk to patients.[6] In the current study, we examined the association between mode of informing patients about the Sprint Fidelis lead advisory and PROs and the association between having an ICD lead subject to an advisory versus no advisory and PROs, as assessed with a broad range of PROs, including both disease-specific and generic measures tapping into patient distress, health status, device concerns, and acceptance.

The mode used to inform ICD patients about the device advisory – that is calling patients in for an urgent clinical follow-up visit versus informing patients ad-hoc during a routine clinical visit – was not associated with psychological well being and health status in our patient cohort, nor was the well being and health status of device advisory patients impaired compared to patients without an advisory notice. In fact, non-advisory controls reported more ICD concerns and poorer mental health status than advisory patients, which is consistent with the findings of a previous study.[13] Concurrent with other studies, these results indicate that ICD patients are generally able to cope with a device advisory.[8,12-14,29] Patients may implicitly accept that with increased complexity of technology to manage heart disease there is a trade off with respect to the risk of complications and hardware malfunctioning. The downloading of the LIA software, which was applicable to all patients with an advice notification in the current study, might also have helped to reinstate patient confidence in the device.[30]

It was somewhat surprising that the mode of notification about the device advisory had no influence on patient well being and health status in our study. A priori, we would have expected that patients receiving a letter calling them in for an urgent clinical follow-up would more likely be in a state of panic and therefore experience more distress than patients being informed about the advisory in a more gentle way during a subsequent clinical follow-up visit. It is possible, however, that the mode of debriefing patients about the device advisory may be of less importance compared to the source of the information (e.g., physician, manufacturer, news media, etc), which information is provided, and whether patients have the possibility to attend psychological counseling, as reported in some studies.[11,12] In the current study, the notification about the device advisory was communicated by physicians. Previously, it has been suggested that patients prefer to learn about a device advisory from their physician rather than from the media.[31] However, the latter study used vignettes and asked patients to rate their concerns with respect to a hypothetical rather than a real device advisory. A more recent study examining the influence of the source of information on patient worry levels showed no overall difference between patients

who heard about the advisory from news media and those who heard about the advisory from a physician, industry, or others.[30] Given the absence of large-scale, well designed studies, it is too premature to draw any firm conclusions about the influence of mode and source of information about the device advisory on patient well being.

Currently, the Heart Rhythm Society has provided recommendations to the industry and physicians with respect to monitoring device performance and how to handle device malfunctioning.[5] Patient recommendations how to deal with a device advisory notification both at an emotional and at an behavioral level are also available.[32] In addition, information on device performance is required to be included in the National Cardiovascular Data Registry (NCDR) ICD Registry in the United States.[5] All these initiatives are of major importance in monitoring device performance and obtaining a true picture of the incidence of hardware malfunctioning and the concomitant risk to patient health. However, given that neither the recommendations from the Heart Rhythm Society nor those from NCDR ICD Registry include PROs – that is asking patients to rate the impact of hardware malfunctioning and device advisories on their well being and quality of life – the risk that the patient is still 'left behind' is prominent, as posited in an editorial to the Sprint Fidelis advisory:[6] "However, in 2008 the important core issues regarding device reliability remain unsolved and longstanding issues regarding patient information and patient well being are even more acute." The inclusion of routine and serial assessments of PROs in national registries such as the NCDR ICD Registry would enable us to track information on how device advisories affect patient well being, rather than relying on information from single-center and smaller scale ad-hoc studies.[8]

The results of the current study should be interpreted with some caution. First, we used a convenience sample as a non-advisory control group. Second, as in previous studies examining the impact of a device advisory notification on patients,[11,12,14] there was a time interval from the notification to patient completion of the PRO measures. It is possible that the advisory notification may have an impact on patient well being and quality of life of patients just after the notification, but that the impact of the advisory dissipates over time, reflecting that patients are able to adapt even short-term. Based on the design of our study, we are not able to deduce whether a short-term effect was present. Third, we did not evaluate patient perception of the risk of having a recalled Sprint Fidelis lead, which could potentially serve as a confounder on PROs. This dimension would be interesting to add to future studies on device advisory notifications, although it may not be patient perception of risk per se but rather whether this knowledge instills fear in and bothers patients that influences PROs. Fourth, the device advisory notification patients differed from the non-advisory patients on time since first ICD implant, with controls having had their ICD for a longer period of time. Time since first ICD implant may serve as a potential confounder on the results, although several studies do not support an influence of duration since implantation

on PROs.[15,33] Fifth, the control cohort was predominantly secondary prevention patients,[15] with the potential that indication might have confounded the results. However, based on the current literature on the impact of indication on PROs, there is no evidence to support this notion, with available studies showing no differences in PROs between primary and secondary prevention patients.[34]

This study also has several advantages. To our knowledge, it is the largest study to date to examine the impact of a device advisory notification on patient well being except for the recently published study by Keren et al.[29] Second, we included a broad spectrum of PROs tapping into patient distress and health status with the use of both disease-specific and generic measures. Disease-specific measures are generally more sensitive to tap symptoms that are relevant to patients and therefore less prone to floor and ceiling effects that may obscure results.[35]

In conclusion, the mode used to inform ICD patients about the Sprint Fidelis lead advisory was not associated with psychological well being and health status, as patients informed about the advisory by letter calling them in for an urgent clinical follow-up visit did not differ on psychological distress and health status from patients informed ad-hoc during a routine clinical visit. We also found no evidence that the well being and health status of device advisory patients is impaired as compared to patients without an advisory notice. Taken together, these results indicate that ICD patients are generally able to cope with a device advisory. Nevertheless, the arrhythmia community should consider the advantages of including routine and serial assessments of PROs in national registries in order to enhance our knowledge of the impact of device advisories on patient well being. If this is implemented as standard practice, with assessments available from the time of implantation, we would not only have a pre advisory assessment but also be able to track patient well being following the advisory over time, and hence to draw more firm conclusions about the impact on patients. For the future management and care of ICD patients, such information would be paramount given that ICD lead failures are likely to be here to stay.

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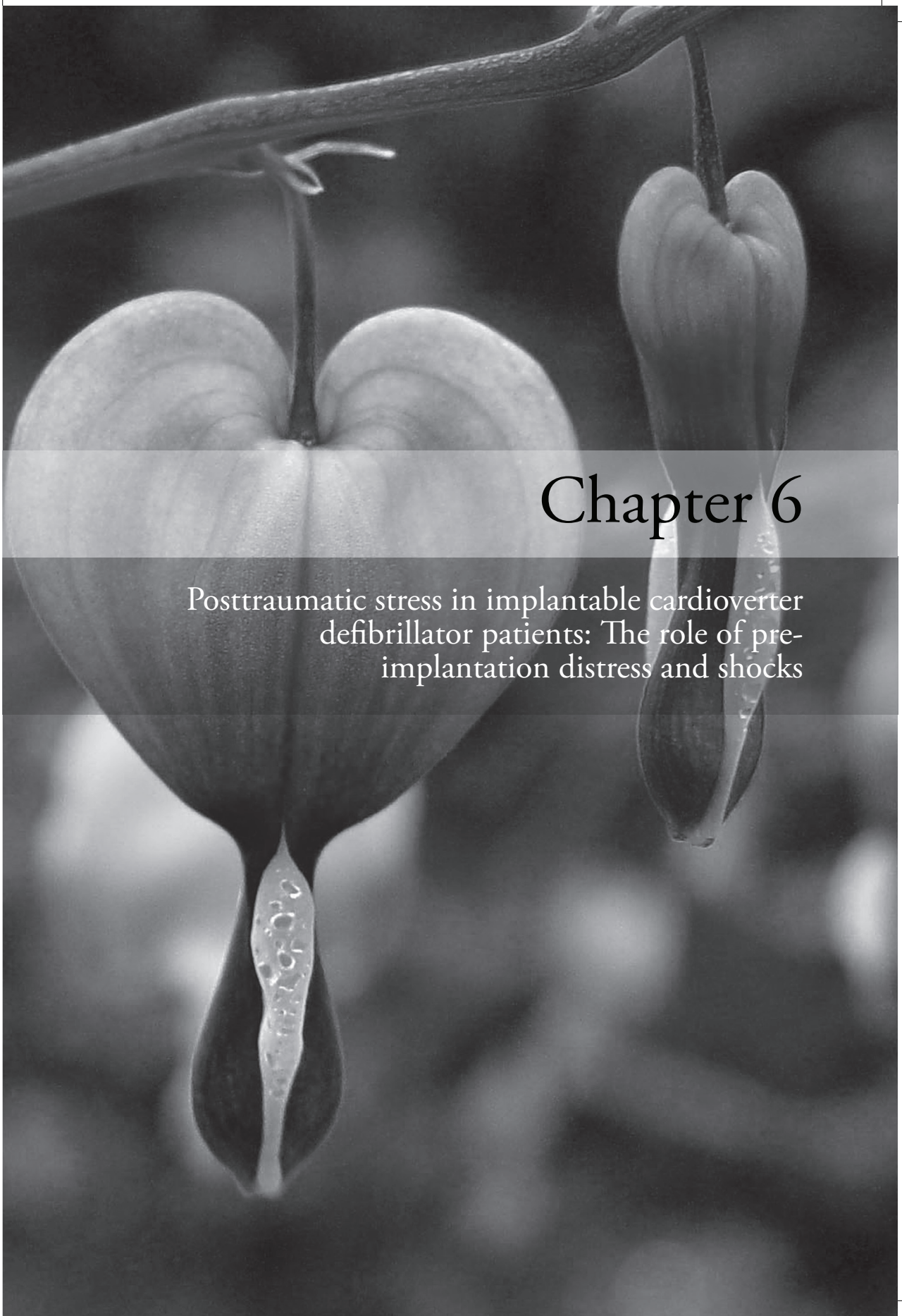

Chapter 6

Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks

ABSTRACT

In this prospective study, we examined the prevalence and determinants of posttraumatic stress disorder (PTSD) in 300 patients (80.3% men, mean age=57.9±12.0) with an implantable cardioverter defibrillator (ICD). At 3 months post implantation, 35 (11.7%) patients qualified for a diagnosis of PTSD. At 6 months, 21 of these patients still had PTSD, while 13 patients had developed new onset PTSD, resulting in a total of 34 (11.3%) patients with PTSD. Multivariable logistic regression analysis showed that Type D personality (OR=2.53, 95% CI:1.05-6.10), high pre-implantation anxiety (OR=2.88; 95% CI:1.10-7.56), and shocks during follow-up (OR=5.78, 95% CI:1.51-22.12) were independently associated with PTSD at 3 months. High pre-implantation anxiety (OR=4.24, 95% CI:1.64-11.00) and ICD concerns (OR=2.73, 95% CI:1.20-6.24) were associated with PTSD at 6 months. To conclude, a small subgroup of ICD patients is at risk of developing PTSD. These patients could be identified by their psychological vulnerability to experience distress prior to implantation. Psychosocial intervention may be warranted in these patients, as PTSD in ICD patients has been associated with an increased risk of mortality.

Versteeg H, Theuns DAMJ, Erdman RAM, Jordaens L, Pedersen SS. Posttraumatic stress in implantable cardioverter defibrillator patients: The role of pre-implantation distress and shocks. Int J Cardiol 2011; 146:438-439.

Subgroups of patients are at risk of posttraumatic stress disorder (PTSD) after a cardiac event, such as a myocardial infarction.[1] Treatment with an implantable cardioverter defibrillator (ICD) may also qualify as a potential traumatic stressor, as it may serve as a constant reminder of the underlying cardiac condition, and is able to deliver an uncontrollable shock to terminate life-threatening ventricular tachyarrhythmias.[2] Two previous studies have reported severe PTSD symptoms in 13-25% of the ICD patients.[3,4] It is essential to identify factors associated with an increased risk of PTSD after ICD implantation, given that severe PTSD symptoms may confer a 3-fold increased risk of mortality in ICD patients, independent of disease severity.[4] To our knowledge, no study to date has examined the determinants of PTSD in ICD patients.

We investigated the prevalence and determinants of PTSD symptoms at 3 and 6 months post implantation, in a sample of 300 ICD patients (80.3% men, mean age=57.9±12.0) participating in the ongoing Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS) at the Erasmus Medical Center, Rotterdam, the Netherlands. The Posttraumatic Stress Diagnostic Scale (PDS) was used to assess symptoms of PTSD (i.e., intrusion, avoidance, and hyperarousal) at 3 and 6 months post implantation.[5] As potential determinants, the distressed (Type D) personality, pre-implantation ICD concerns, anxiety, depression, age, sex, partner, ischemic etiology, shocks during follow-up, previous myocardial infarction, diabetes, smoking, and use of psychotropic medication, were included in logistic regression analyses.

At 3 months post implantation, 35 (11.7%) patients met the symptom criteria for a diagnosis of PTSD. Three months later, 21 (60%) of these patients still qualified for PTSD, while 13 patients had developed new onset PTSD, resulting in a total of 34 (11.3%) patients with PTSD 6 months post implantation. Table 1 shows that Type D personality, high pre-implantation anxiety, and shocks during follow-up were independent determinants of PTSD at 3 months. At 6 months, only high pre-implantation ICD concerns and anxiety were significant determinants of PTSD, adjusting for demographic, clinical, and the other psychological factors.

Despite ICD treatment being well accepted by the majority of patients, a subgroup of patients is at risk of developing symptoms of PTSD after implantation. At 3 months post implantation, ICD shock was the strongest determinant of PTSD, while pre-implantation anxiety and ICD concerns, but not shocks, were associated with PTSD at 6 months. These findings conform with previous studies acknowledging the importance of the patient's psychological profile[6,7] and shocks in determining post implantation distress.[8,9] Early identification and treatment of patients' fears and concerns might be beneficial,[10] as PTSD symptoms have been associated with impaired health status and poor prognosis in cardiac patients.[4,11]

Some limitations must be acknowledged. First, the PDS is a self-report measure that may overestimate the prevalence of PTSD.[12] However, it has been validated

against a structural interview and mirrors the DSM-IV criteria for a PTSD diagnosis.[5] Second, we had no information on PTSD symptoms prior to ICD implantation, yet patients were asked to rate the items on the PDS with respect to their ICD ensuring that PTSD could not be due to other traumatic events. Third, the follow-up period only extended to 6 months, with studies needed to examine the trajectory and determinants of PTSD symptoms after ICD implantation in the long term. Strengths include the prospective design and relatively large sample size.

In conclusion, the findings of this study indicate that a small subgroup of ICD patients is at risk of developing PTSD, and that these patients might be identified by their psychological vulnerability to experience distress prior to implantation. Psychosocial intervention may be warranted in this subset of patients.

Table 1. Variables associated with PTSD at 3 and 6 months

	PTSD at 3 months			PTSD at 6 months		
	OR	**[95% CI]**	***p***	**OR**	**[95% CI]**	***p***
Psychological factors[a] (pre-implantation)						
Type D personality	2.53	1.05-6.10	.04*	0.81	0.31-2.15	.67
ICD concerns	1.76	0.75-4.13	.19	2.73	1.20-6.24	.02*
Anxiety	2.88	1.10-7.56	.03*	4.24	1.64-11.00	.003**
Depression	1.10	0.42-2.88	.85	0.93	0.34-2.59	.89
Demographics						
Age	0.98	0.94-1.01	.23	0.99	0.95-1.03	.62
Female sex	1.30	0.50-3.42	.59	1.01	0.36-2.81	.99
Having a partner	1.07	0.24-4.83	.93	1.66	0.31-8.95	.56
Clinical factors						
Ischemic etiology	0.53	0.10-2.86	.46	0.69	0.12-3.78	.66
ICD shock during follow-up	5.78	1.51-22.12	.01**	0.88	0.09-8.23	.91
Previous MI	1.71	0.33-8.81	.52	2.70	0.52-13.86	.24
Diabetes	0.62	0.17-2.25	.47	0.41	0.10-1.67	.21
Smoking	2.75	0.95-8.01	.06	1.87	0.59-5.95	.29
Psychotropic medication	1.58	0.61-4.04	.34	1.81	0.73-4.54	.20

Multivariable logistic regression analysis
[a] Psychological variables were entered as dichotomous variables
*$p \leq .05$; **$p \leq .01$
ICD=implantable cardioverter defibrillator; MI=myocardial infarction

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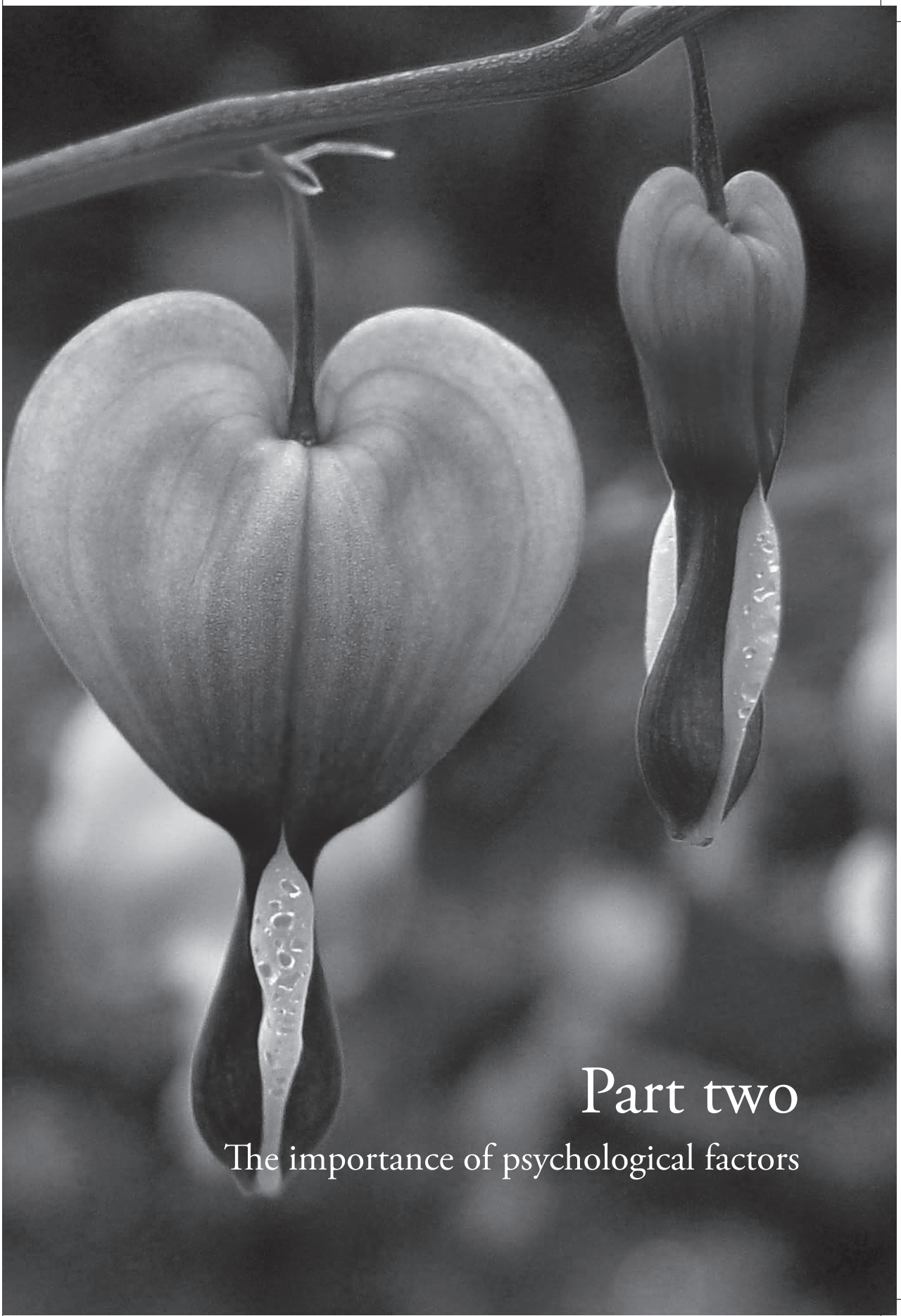
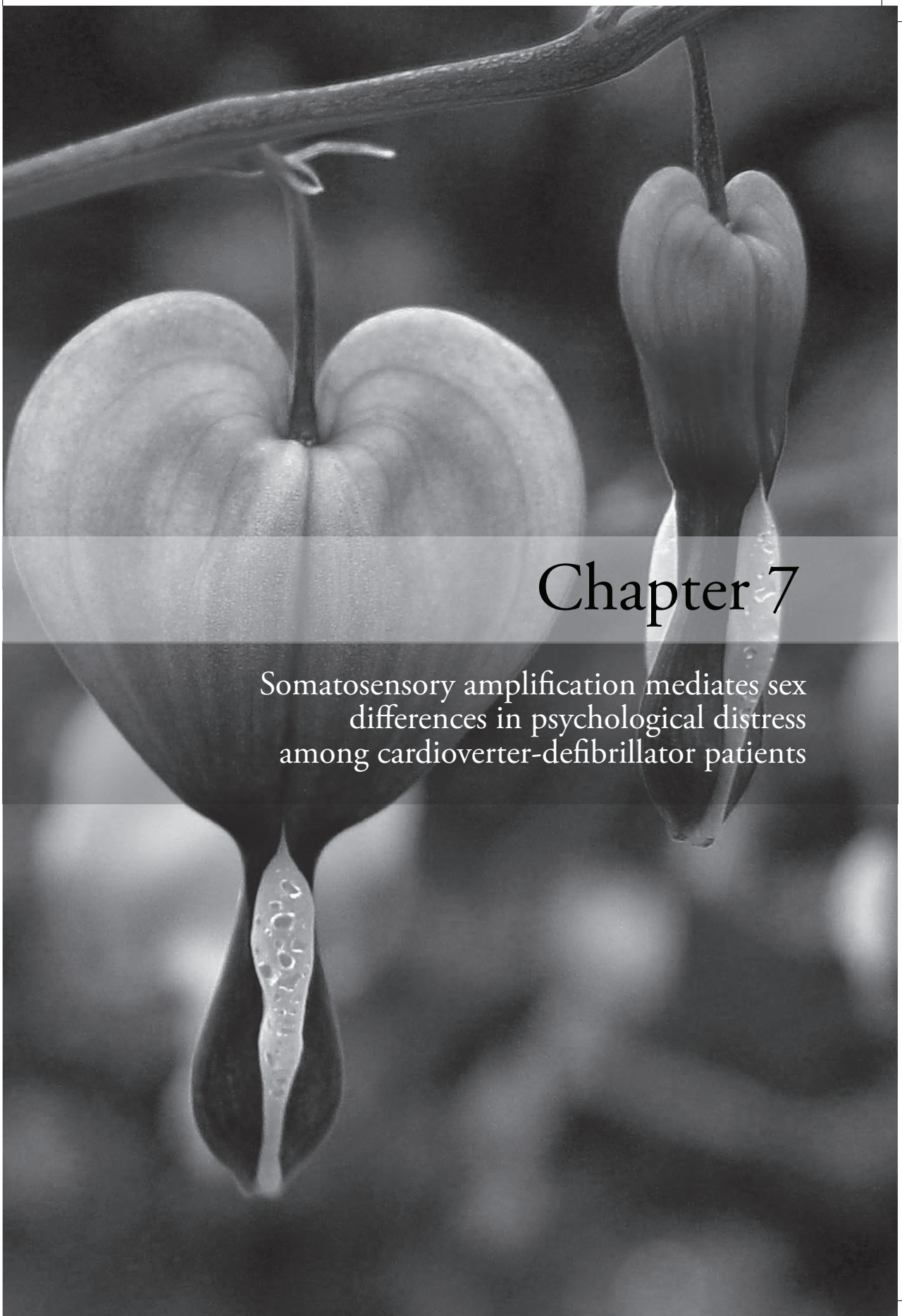


Part two

The importance of psychological factors



Chapter 7

Somatosensory amplification mediates sex differences in psychological distress among cardioverter-defibrillator patients

ABSTRACT

Objective The present study examined whether female patients with an implantable cardioverter defibrillator (ICD) report more psychological distress than male patients, and whether somatosensory amplification mediates this relationship.

Methods Consecutive ICD patients (*N*=241, 33% women) participating in the Living with an Implanted Cardioverter-Defibrillator (LICAD) Study, completed the Symptom Checklist-90 (SCL-90) and Somatosensory Amplification Scale (SSAS).

Results Univariable linear regression analyses showed that female ICD patients reported more symptoms of anxiety (ß=.13, *p*=.04), phobic anxiety (ß=.13, *p*=.05), and somatic health complaints (ß=.15, *p*=.02), and scored higher on somatosensory amplification (ß=.24, *p*<.001) than men. Multivariable regression analyses, adjusted for demographic and clinical risk factors, revealed that somatosensory amplification was associated with more anxiety (ß=.48, *p*<.001), phobic anxiety (ß=.34, *p*<.001), and somatic health complaints (ß=.49, *p*<.001). Sobel tests indicated that somatosensory amplification mediated the association between sex and these 3 domains of psychological distress (*p*=.0005, .002 and .0006, respectively).

Conclusions Somatosensory amplification mediated the relationship between female sex and heightened anxiety, phobic anxiety, and somatic health complaints in ICD patients. Women may be more likely to misinterpret bodily sensations as indicative of deterioration in their condition. Interventions focusing on modifying these dysfunctional beliefs may reduce their psychological distress.

Versteeg H, Baumert J, Kolb C, Pedersen SS, Denollet J, Ronel J, Ladwig KH. Somatosensory amplification mediates sex differences in psychological distress among cardioverter-defibrillator patients Health Psychol 2010;29:477-483.

INTRODUCTION

In the general cardiovascular literature and in epidemiological studies, women are known to report more psychological distress compared to men.[1,2] Female sex has also been thought to be an independent risk factor for anxiety, depression, and impaired quality of life in patients treated with implantable cardioverter defibrillator (ICD) therapy.[3-5] However, the few available studies on the influence of sex on psychological distress in ICD recipients are based on a relatively small number of women and show contradicting results.[6]

Besides symptoms of psychological distress, health surveys and studies on physical symptom reporting have consistently found that women report more somatic symptoms compared to men.[7,8] One explanation for this phenomenon may be that women are more aware of, and more attentive to, weak or diffuse bodily sensations.[7] This heightened selective attention to bodily sensations may lead to reactions of affect and cognitions that intensify them.[7] Barsky and colleagues described these individuals as *somatosensory amplifiers*: persons with a tendency to perceive normal somatic and visceral sensations as unusually intense, noxious, and disturbing.[9] Somatosensory amplification involves three elements: 1) bodily hypervigilance; 2) a tendency to focus on certain relatively weak and infrequent bodily sensations; and 3) the disposition to appraise them as abnormal and symptomatic of disease rather than normalizing them.[9]

Two studies have shown that Japanese women scored significantly higher on somatosensory amplification than Japanese men, even after adjusting for age, somatic symptoms, and mood states.[10,11] Among functional dyspepsia patients, female subjects had significantly higher somatosensory amplification scores than male subjects.[12] Several studies suggest that somatosensory amplification may not only be associated with the reporting of somatic symptoms, but also with negative affectivity and general distress, including symptoms of depression, anxiety, hostility, and decreased quality of life.[9,12,13]

Taken together, evidence suggests that both female sex and somatosensory amplification are related to symptoms of psychological distress. Females may score higher on somatosensory amplification, which in turn may increase the risk of psychological difficulties, suggesting that somatosensory amplification may mediate the relationship between female sex and heightened psychological distress. Hence, the objective of the present study was to investigate whether women implanted with an ICD report more psychological distress than men, and whether somatosensory amplification mediates this relationship. This knowledge might help physicians to better understand and manage patients whose reported psychological symptoms do not match their clinical condition, with a view to providing adjunctive intervention and treatment.[14]

METHODS

Study design and participants

Consecutive patients (*N*=251) implanted with an ICD, participating in the Living with an Implanted Cardioverter-Defibrillator (LICAD) Study, comprised the patient sample for the current study. Patients attending the cardiology outpatient clinic of the German Heart Center Munich for routine ICD check-up participated in the baseline examination between January and May 1998 (first survey, *n*=148) and between April and June 2002 (second survey, *n*=54). Because the sample of the first and second surveys included only 17.3% female ICD patients, the LICAD survey was extended in 2002 and 2003 including only female patients (*n*=49). Patients were not included if their first ICD implantation was <3 months ago (to avoid benign transitory adaptation reactions), if they were <16 years of age, or had severe cognitive impairments. Overall, of 265 patients meeting the criteria, 14 (5.3%) refused to participate, leading to an initial patient sample of 251 patients. During their visit for routine ICD check-up at the outpatient clinic, patients underwent a variety of additional clinical, psychometric, and psychophysiological tests as part of the LICAD study. Among these, patients were asked to complete a set of standardized and validated psychological questionnaires. For the current study, 10 patients were excluded due to missing data on self-report measures. Hence, analyses were based on 241 (96%) patients (67% men, mean age=58.5±13.9 years). The dropout analysis revealed no systematic differences in baseline characteristics between the non-responders and responders.

The study was conducted according to the Helsinki Declaration, and written informed consent was obtained from all patients. The study was approved by the ethics committee of the Medical Faculty of the Technical University of Munich, Germany.

Measures

Demographic and clinical variables

Information on clinical variables, including specific data regarding ICD treatment, was obtained from the patient records at the pacemaker outpatient clinic of the German Heart Center Munich. Left ventricular ejection fraction (LVEF) was assessed echocardiographically or angiograpically, and was classified into 3 categories (≥55%, 35% to 54%, or <35%). Demographic characteristics were assessed in a standardized interview. Patients were also asked if they had experienced cardiac symptoms (palpitations, tachycardia, racing heart) or chest pain (at rest, at night, during exertion) in the last 4 weeks before the examination.

Psychological distress

The German version of the Symptom Checklist-90 (SCL-90),[15] a multidimensional self-report questionnaire, was used to measure psychological symptom status with a time reference of "the past 7 days including today". Each item is rated on a 5-point

Likert scale, ranging from 'not at all' (0) to 'extremely' (4). We included items from the following domains: Anxiety (10 items), Depression (14 items), Phobic Anxiety (7 items), and Anger-Hostility (6 items). In addition, 12 items on Somatic Health Complaints (e.g. heart/chest pain, headache, soreness of muscles, tingling of a part of the body) were included. For all domains, a missing value of an item was replaced with the mean of the other items, if at least 70% of the items of the subscale were completed.

Somatosensory amplification

Somatosensory amplification was assessed with the Somatosensory Amplification Scale (SSAS),[13] which was translated into German according to standard practice. It is a 10-item self-report questionnaire asking the respondents to rate the degree to which each statement is 'characteristic of you in general', on an ordinal scale from 1 to 5. The items cover a range of uncomfortable bodily sensations (e.g., hunger contractions, being too hot or too cold), most of which generally do not connote serious disease. The total score ranges from 10 to 50, with a higher score indicating greater symptom amplification. The original SSAS has adequate internal consistency (Chronbach's alpha=.82), and a considerable test-retest reliability (r=.79 over a median interval of 74 days).[13] Cronbach's alpha was .65 in the current sample.

Statistical analyses

Prior to investigating whether somatosensory amplification mediates the relationship between sex and psychological distress (as assessed with the SCL-90), we examined whether the assumptions underlying the mediation model according to Baron and Kenny (1986) were fulfilled: (a) Sex had to be associated with the domains of psychological distress; (b) sex had to be related to the hypothesized mediator somatosensory amplification; and (c) somatosensory amplification had to be associated with psychological distress, controlling for sex. Somatosensory amplification was considered a mediator if it accounted for the relation between sex and psychological distress. The assumptions for mediation were tested using a series of linear regression models. To allow for a more direct test of the mediation effect, Sobel tests were also conducted.[16] Sobel tests, which are products of coefficient tests for the mediating variable effect, are used to test the significance of the mediating variable effect by dividing the estimate of the mediating variable effect by its standard error and comparing this value to a standard normal distribution. In contrast with causal step methods (e.g. the Baron and Kenny approach), Sobel tests are less prone to Type I errors and have more statistical power to detect mediation.[17] Multivariable linear regression analyses were performed to adjust for the potential confounding effects of demographic and clinical risk factors on psychological distress. A priori based on the literature, age, marital status (single *versus* married/partner), educational level (secondary school

or less *versus* high school/university degree), time since implantation, ICD shocks (≥1), New York Heart Association (NYHA) functional class (class I-II *versus* class III-IV), LVEF (<35% *versus* ≥35%), resuscitation, coronary heart disease (CHD) or myocardial infarction (MI), smoking, and psychotropic medication, were selected as covariates besides sex. Sobel tests were performed with an SPSS macro by Preacher and Hayes (http://www.comm.ohio-state.edu/ahayes/ sobel.htm),[18] as SPSS does not provide the possibility to directly test the mediation effect. SPSS for Windows, version 17.0, was used for all other analyses. A *p*-value equal to or less than .05 was considered to be statistically significant.

RESULTS

Baseline characteristics stratified by sex

Baseline characteristics stratified by sex are presented in Table 1. Compared to men, female ICD patients were on average younger (55.04 *versus* 60.29 years, *p*=.01), less likely to be living with a partner (57.1% *versus* 79.2%, *p*<.001), to have marked limitations in physical activity (NYHA class III or IV: 15.2% *versus* 29.2%, *p*=.02), to be diagnosed with CHD or MI (36.3% *versus* 70.8%, *p*<.001) or hypercholesterolemia (26.6% *versus* 39.85, *p*=.05), but more likely to have been resuscitated (71.3% *versus* 55.9%, *p*=.02), to have a LVEF of ≥55% (36.8% *versus* 18.1%, *p*=.002), to have experienced cardiac symptoms in the past 4 weeks (41.3% *versus* 23.0%, *p*=.003), and to be prescribed psychotropic medication (11.4% *versus* 3.7%, *p*=.04). No other statistically significant sex differences were found on demographic and clinical baseline characteristics.

Table 1. Baseline characteristics for the total sample (*N*=241) and stratified by sex

	Missing	Total sample (*N*=241)	Men (*n*=161)	Women (*n*=80)	*p*
Demographics					
Age, mean (SD)[a]	0	58.55 (13.94)	60.29 (12.58)	55.04 (15.84)	.01*
Marital Status	5				<.001***
Single		30 (12.7)	19 (11.9)	11 (14.3)	
Married/living with partner		170 (72.0)	126 (79.2)	44 (57.1)	
Divorced/ widowed		36 (15.3)	14 (8.8)	22 (28.6)	
Educational level	5				.37
≤ Secondary school		130 (55.1)	90 (57.7)	40 (50.0)	
High school education		45 (19.1)	26 (16.7)	19 (23.8)	
University degree		61 (25.8)	40 (25.6)	21 (26.3)	
Currently employed	4	66 (27.8)	47 (29.6)	19 (24.4)	.40

Clinical factors					
Time since implantation	1				.21
3-6 months		36 (15.0)	19 (11.8)	17 (21.5)	
7-12 months		27 (11.3)	17 (10.6)	10 (12.7)	
13-24 months		61 (25.4)	41 (25.5)	20 (25.3)	
25-48 months		83 (34.6)	58 (36.0)	25 (31.6)	
>48 months		33 (13.8)	26 (16.1)	7 (8.9)	
NYHA class III/IV	1	59 (24.6)	47 (29.2)	12 (15.2)	.02*
LVEF	5				.007**
≥55%		57 (24.2)	29 (18.1)	28 (36.8)	
35% to 54%		104 (44.1)	77 (48.1)	27 (35.5)	
<35%		75 (31.8)	54 (33.8)	21 (27.6)	
CHD/MI	0	143 (59.3)	114 (70.8)	29 (36.3)	<.001***
Resuscitation	0	147 (61.0)	90 (55.9)	57 (71.3)	.02*
ICD shocks	1				.13
0		132 (55.0)	83 (51.6)	49 (62.0)	
1-4		66 (27.5)	45 (28.0)	21 (26.6)	
5-9		24 (10.0)	21 (13.0)	3 (3.8)	
≥10		18 (7.5)	12 (7.5)	6 (7.6)	
Cardiac symptoms in past 4 weeks[b]	0	70 (29.0)	37 (23.0)	33 (41.3)	.003**
Angina pectoris in past 4 weeks	0	60 (24.9)	40 (24.8)	20 (25.0)	.98
Psychotropic medication	1	15 (6.3)	6 (3.7)	9 (11.4)	.04*
Smoking	6	21 (8.9)	15 (9.6)	6 (7.6)	.61
Comorbidities					
Hypertension	0	50 (20.7)	30 (18.6)	20 (25.0)	.25
Diabetes mellitus	0	26 (10.8)	15 (9.3)	11 (13.8)	.30
Hypercholesterolemia[c]	1	85 (35.4)	64 (39.8)	21 (26.6)	.05*
Renal failure	0	18 (7.5)	13 (8.1)	5 (6.3)	.61
Stroke	0	12 (5.0)	8 (5.0)	4 (5.0)	.99

Results are presented as *n* (%), unless otherwise stated.
[a] *t* test; Chi-square test for all others
[b] Palpitations, tachycardia, and racing heart
[c] Patients taking lipid-lowering medication
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$
CHD=coronary heart disease; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association functional class; MI=myocardial infarction

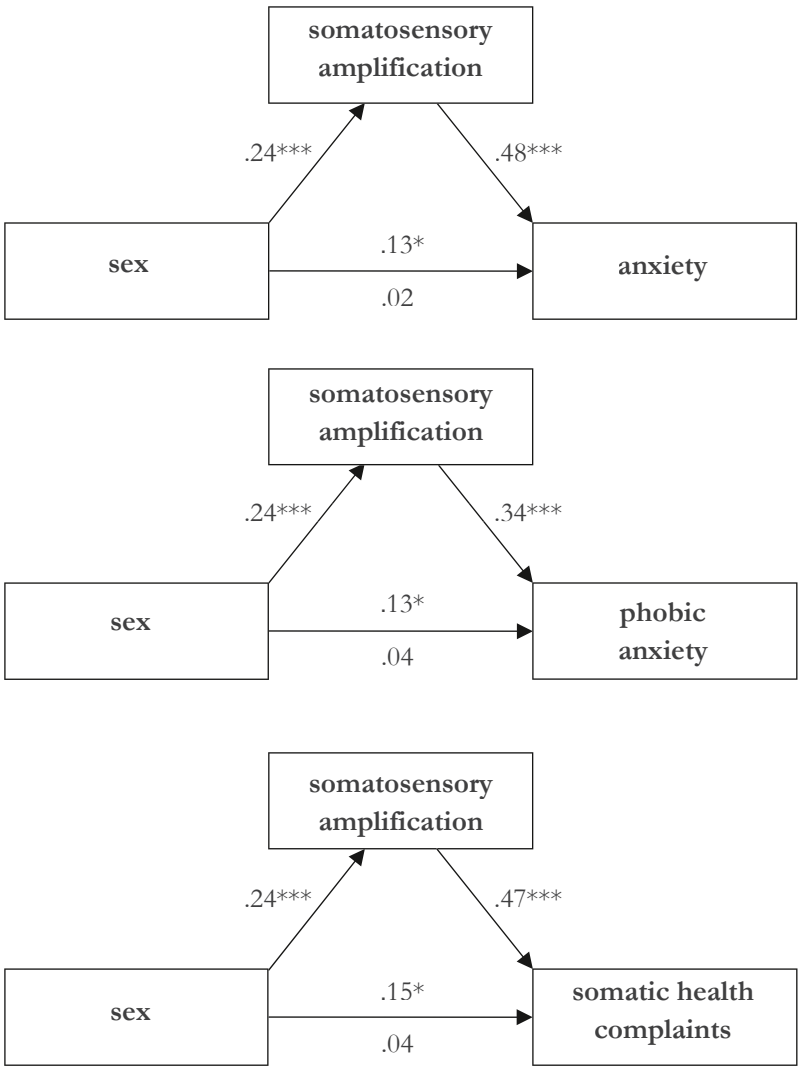
Test of the Mediation Model

We tested the hypothesis that somatosensory amplification mediated the relationship between sex and psychological distress for each domain of the SCL-90, using a series of linear regression analyses. Results indicated that female sex was significantly related to more Anxiety (ß=.13, p=.04, R^2=.02), Phobic Anxiety (ß=.13, p=.05, R^2=.02), and Somatic Health Complaints (ß=.15, p=.02, R^2=.02), but not to Depression and Hostility (Table 2). The second assumption underlying the mediation model was also fulfilled: sex was significantly associated with somatosensory amplification (ß=.24, p<.001, R^2=.06), with women scoring higher on the SSAS than men (25.84±7.03 *versus* 22.52±5.95). As the first assumption for mediation was not fulfilled for Depression and Hostility, the third assumption was solely examined for Anxiety, Phobic Anxiety, and Somatic Health Complaints. Multivariable linear regression analysis showed that a higher score on somatosensory amplification was associated with significantly more Anxiety (ß=.48, p<.001, ΔR^2=.22), Phobic Anxiety (ß=.34, p<.001, ΔR^2=.11), and Somatic Health Complaints (ß=.47, p<.001, ΔR^2=.21), controlling for sex. Once somatosensory amplification was included in the model, the effect of sex on Anxiety, Phobic Anxiety, and Somatic Health Complaints was no longer significant (p=.80, .50, and .49, respectively), indicating perfect mediation (Figure 1). Sobel tests were performed to examine whether the indirect effect of sex on psychological distress via somatosensory amplification was significantly different from zero. The results showed that somatosensory amplification significantly mediated the relation between sex and Anxiety (z'=3.46, p=.0005), Phobic Anxiety (z'=3.11, p=.002), and Somatic Health Complaints (z'=3.45, p=.0006).

Table 2. Mean scores of men and women on the SCL-90 domains

	Men mean (SD)	Women mean (SD)	B	SE B	ß	R^2
Anxiety	4.30 (4.28)	5.61 (5.48)	0.13	0.64	.13*	.02*
Phobic Anxiety	2.43 (3.00)	3.39 (4.59)	0.95	0.49	.13*	.02*
Depression	7.35 (6.07)	8.81 (8.64)	1.46	0.96	.10	.01
Hostility	2.56 (2.53)	2.59 (2.93)	0.04	0.37	.01	.00
Somatic Health Complaints	7.00 (6.07)	9.13 (7.44)	2.13	0.88	.15*	.02*

Figure 1. Mediation models for sex, somatosensory amplification, and anxiety/ phobic axiety /somatic health complaints



ß coefficients for sex are direct effects above the path and mediated effects below the path.
*$p \leq .05$; ***$p \leq .001$

Table 3. Multivariable linear regression analyses

	Anxiety				Phobic Anxiety				Somatic Health Complaints			
	B	**SE B**	**ß**	**ΔR^{2a}**	**B**	**SE B**	**ß**	**ΔR^{2a}**	**B**	**SE B**	**ß**	**ΔR^{2a}**
Somatosensory amplification	0.33	0.04	.48***	.194	0.19	0.03	.37***	.116	0.48	0.06	.49***	.206
Female sex	-0.58	0.67	-.06	.003	-0.08	0.52	-.01	.000	1.19	0.91	.09	.005
Age	0.03	0.02	.08	.004	0.04	0.02	.17*	.019	0.07	0.03	.16*	.017
Partner	-0.33	0.63	-.03	.001	-0.38	0.48	-.05	.002	-0.35	0.86	-.03	.001
High school/university	-0.39	0.64	-.04	.001	-0.40	0.49	-.05	.003	-0.48	0.87	-.03	.001
Time since implantation	0.00	0.01	.01	.000	0.00	0.01	.02	.000	0.01	0.02	.03	.001
ICD shocks (≥1)	0.12	0.57	.01	.000	0.58	0.44	.09	.007	-1.02	0.77	-.08	.006
NYHA III/IV	0.48	0.68	.05	.002	0.21	0.52	.03	.001	1.69	0.92	.11	.011
LVEF (<35%)	-0.23	0.61	-.02	.000	0.72	0.47	.10	.009	1.02	0.83	.08	.005
Resuscitation	0.10	0.57	.01	.000	0.65	0.43	.10	.008	0.11	0.77	.01	.000
CHD/MI	-1.06	0.64	-.11	.009	0.01	0.49	.00	.000	0.53	0.87	.04	.001
Smoking	0.46	1.00	.03	.001	0.94	0.77	.08	.006	1.53	1.36	.07	.004
Psychotropic medication	2.36	1.13	.13*	.015	1.06	0.86	.08	.006	0.94	1.53	.04	.001

[a]ΔR^2 compared to the model including all other variables; R^2 for the full model is .28, .21 and .33, respectively (*ps*<.001)

*$p \leq .05$; ***$p \leq .001$

CHD=coronary heart disease; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association functional class; MI=myocardial infarction.

In extended multivariable linear regression analyses, somatosensory amplification remained significantly associated with more Anxiety (ß=.48, p<.001, ΔR^2=.19), Phobic Anxiety (ß=.37, p<.001, ΔR^2=.12), and Somatic Health Complaints (ß=.49, p<.001, ΔR^2=.21), controlling for demographic and clinical variables (Table 3). None of the demographic and clinical variables were related to Anxiety, Phobic Anxiety, and Somatic Health Complaints, including shocks (ß=.01, p=.84; ß=.09, p=.19, and ß=-.08, p=.19, respectively), except for usage of psychotropic medication, which was associated with more Anxiety (ß=.13, p=.04, ΔR^2=.02), and older age, which was associated with more Phobic Anxiety (ß=.17, p=.03, ΔR^2=.02), and Somatic Health Complaints (ß=.16, p=.02, ΔR^2=.02). Of note, when shocks were examined in a continuous manner or with a cut-off of ≥5 shocks, the results did not change.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the role of somatosensory amplification as a mediator between female sex and heightened psychological distress in ICD patients. Results from the univariable linear regression analyses showed that female ICD patients reported more symptoms of anxiety, phobic anxiety, and somatic health complaints (R^2=.02), and scored significantly higher on somatosensory amplification (R^2=.06) than male ICD patients. In multivariable analyses, somatosensory amplification accounted for about 20% of the variance in anxiety and somatic health complaints, and over 10% of the variance in phobic anxiety scores, while sex was no longer significantly associated with any of these domains. This indicates that somatosensory amplification mediated the relationship between female sex and heightened anxiety, phobic anxiety, and somatic health complaints in ICD patients, which was also confirmed by Sobel tests.

The current results show that women with an ICD report more somatic health complaints than men, which is consistent with previous research.[19] Female ICD patients also experienced more anxiety but not depression, which is in accordance with some,[3,20] but not all studies.[21-23] The majority of these studies might have been insufficiently powered to adequately detect sex differences on distress outcomes.

Men tend to have different health attitudes than women; women seem to be more involved with health and illness issues and often have more responsibility in taking care of ill relatives.[24] This might result in a higher selective attention to their body and a greater tendency to intensify bodily sensations and attribute them to physical illness.[7] These are characteristic elements of somatosensory amplification.[9] Accordingly, the current study confirms earlier results that women are more likely to be somatosensory amplifiers than men,[10-12] but it also extends previous research by showing that somatosensory amplification may explain sex differences in levels of anxiety, phobic anxiety, and somatic health complaints in ICD patients.

Somatosensory amplification was associated with more somatic health complaints

and (phobic) anxiety while taking into account demographic and clinical variables, including LVEF and ICD shocks. This suggests that the self-reported tendency to amplify may be related to the variability in psychological distress among ICD patients, independent of the objective severity of the underlying cardiac disease and ICD therapy. In fact, female ICD patients reported more cardiac symptoms, somatic health complaints, and anxiety than men, while their condition was generally less severe as indicated by NYHA functional class and LVEF. Although shocks have previously been shown to increase the risk of psychological distress and impaired quality of life,[3,25] this was not confirmed by the present results and several other studies.[26,27] These findings suggest that it may be timely to expand our focus beyond shocks as the sole determinant of psychological distress in ICD patients.

Several studies have failed to find a relationship between somatosensory amplification and heartbeat detection ability or pain sensitivity, suggesting that somatosensory amplification may not be caused by heightened physiological sensitivity.[28-30] Rather, somatosensory amplification may be the result a disturbance in the awareness and interpretation of bodily sensations, which is confirmed by preliminary results from an electroencephalographic (EEG) study showing a significant relationship between somatosensory amplification and parameters of auditory event-related potentials reflecting cognitive processing of sensory input.[31] The amplifying perceptual and cognitive style has been emphasized as a risk factor for somatoform disorders, e.g. hypochondria - an obsessive and enduring preoccupation with the fear or belief that one has a serious illness.[13] ICD patients with a tendency toward somatosensory amplification could experience their bodily sensations as so intense and disturbing, that they may hold the dysfunctional belief that these sensations are signs of disease or deterioration in their condition.[32] Educational and psychological interventions are needed that focus on correcting the attributional errors of somatosensory amplifiers. A limited number of trials have demonstrated that cognitive-behavioral therapy (CBT) can effectively reduce amplification of somatic symptoms in individuals with atypical chest pain, palpitations, and hypochondria.[33-36] CBT as mainstay of treatment, or in combination with cardiac rehabilitation, has also been shown to be beneficial in reducing anxiety in ICD patients.[37] More research is needed to see if CBT is (cost-)effective in reducing psychological distress and adverse secondary outcomes in ICD patients.

The results of the current study should be interpreted with some caution due to the following limitations. First, the cross-sectional study design does not permit conclusions about the direction of causality between somatosensory amplification and psychological distress. It is possible that psychological distress causes ICD patients to amplify their bodily sensations. This interpretation might, however, be somewhat less likely than the converse, as the SSAS has considerable test-retest reliability, indicating that somatosensory amplification is more a trait than a state measure.[13] Moreover, the

instruction of the SCL-90 calls for the rating of psychological distress in the past 7 days, while the instruction on the SSAS asks the patient to consider how characteristic each item is of him/her generally.[9] Another limitation of the cross-sectional design is the absence of information on the level of psychological distress before the ICD implantation. In addition, because of the lack of a healthy control group, it remains unclear whether the differences in psychological distress are preexisting in men and women in general, or if they reflect differences in adjustment to the cardiac disease condition or ICD implantation. Prospective, longitudinal studies are essential to address these questions adequately. Second, some authors have suggested that the SSAS is more likely an index of psychological distress than a valid measure of somatic sensitivity.[28] However, the SSAS has been shown to predict somatic symptom reporting independent of, and in addition to, the presence of a physical illness and the level of anxiety and depression.[38,39] Third, we used a generic, multidimensional scale (SCL-90) to assess psychological distress. In order to replicate the current findings with potentially more sensitive measures, it would be important to include disease-specific measures in future research. Finally, based on a theoretical rationale the current study examined somatosensory amplification as a potential mediator, but other psychological variables, for example, anxiety sensitivity and coping behavior, may also explain the sex differences in psychological distress.[40,41] Future studies are needed to investigate the potential role of other mediators. This study also has several strengths, including the relatively large sample size and the use of Sobel tests, which allowed for a direct test of the mediational role of somatosensory amplification with greater statistical power and less susceptibility to Type I error rates than other formal methods of assessing mediation.[18]

In conclusion, somatosensory amplification mediated the relationship between female sex and heightened self-reported anxiety, phobic anxiety, and somatic health complaints after ICD implantation, independent of demographic and clinical risk factors, including ICD shocks. This suggests the need to take possible effects of somatosensory amplification into account when studying sex differences in psychological distress among ICD patients. Female ICD patients may be more likely to perceive normal bodily sensations as unusually intense and indicative of deterioration in their condition. Education and psychological interventions, such as CBT, focusing on modifying these dysfunctional beliefs may reduce their levels of psychological distress. Future research is needed to confirm the findings of the current study using a prospective study design.

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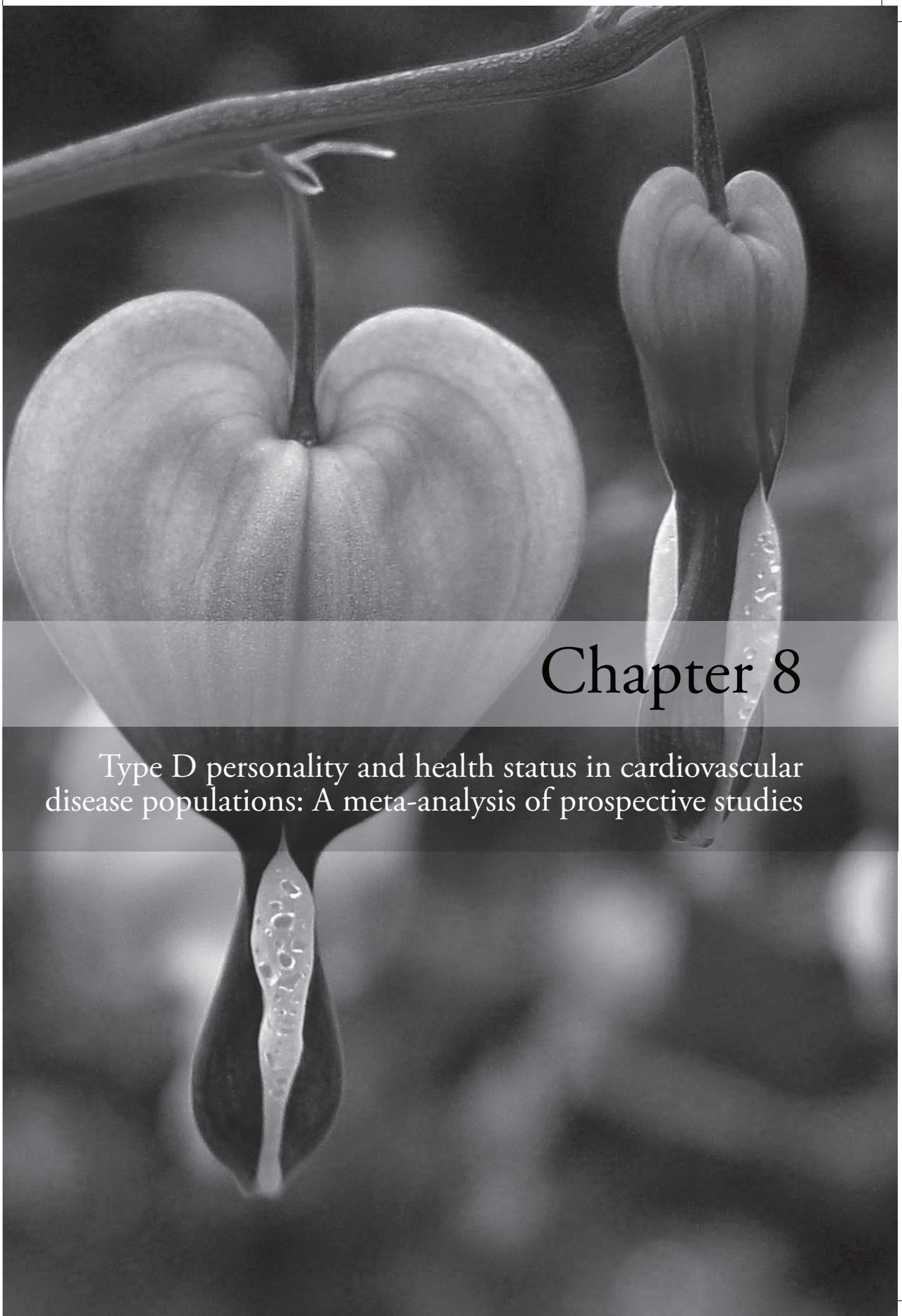

Chapter 8

Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies

ABSTRACT

Background Knowledge of the factors associated with individual differences in patient reported outcomes is essential to identify high-risk patients and improve secondary prevention. The objective of this meta-analysis was to examine the association between Type D personality and the individual differences in patient reported physical and mental health status among cardiovascular patients.

Methods A computerized search of the literature through PUBMED and PsychINFO (1995-May 2011) was performed and prospective studies were selected that analyzed the association between Type D personality and health status in cardiovascular patients. Two separate meta-analyses were performed for the association of Type D personality with physical and mental health status, respectively.

Results Of all identified studies, 10 studies met the selection criteria. The meta-analyses showed that Type D was associated with a 2-fold increased odds for impaired physical health status (3035 patients, OR=1.94, 95% CI:1.49-2.52) and a 2.5-fold increased odds for impaired mental health status (2213 patients, OR=2.55, 95% CI:1.57-4.16). There was no significant heterogeneity between the studies on physical health status (Q=12.78, p=.17, I^2=29.59), but there was between those on mental health status (Q=21.91, p=.003, I^2=68.04). Subgroup analyses showed that the association between Type D and mental health status decreased yet remained significant when adjusting for baseline mental health status.

Conclusions Type D personality was shown to be an independent correlate of impaired patient reported physical and mental health status in various cardiovascular patient groups. Clinicians should be aware of the association between chronic psychological distress and poor patient reported outcomes.

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INTRODUCTION

Patients with cardiovascular disease often experience a substantial degree of physical and psychosocial difficulties that lead to impairments in perceived health status.[1,2] Health status refers to patient's perceptions of how their disease affects their function, symptoms and quality of life.[3] Physical health status concerns the effect of disease on physical functioning including walking, climbing stairs, and household work; mental health status refers to effects on psychological well-being, social functioning, and vitality.

Patient reported outcomes have gained increased recognition in cardiovascular disease.[4] Poor patient reported health status has been associated with an increased risk of mortality and rehospitalization independent of disease severity.[5,6] However, large individual differences exist in patient reported health status, which do not necessarily concur with the physician's evaluation of the patient's health,[7] or with the patient's objective clinical status.[8,9] Rather, patients with similar conditions and disease severity may have distinct perceptions of their health,[10] which should be taken into account in clinical practice.

Understanding individual differences in patient reported outcomes is crucial in order to identify high-risk patients and improve patient-centered care.[11] In addition to clinical and demographic factors, psychological factors may be associated with the perceived health status of cardiovascular patients,[12,13] with the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits) being one such factor.[14] Type D individuals experience a broad range of negative emotions and tend to inhibit self-expression in social interaction.[15] Type D has been associated with increased mortality and morbidity in various cardiovascular populations independent of standard biomedical risk factors.[16,17]

The objective of this meta-analysis was to examine the association between Type D personality and the individual differences in patient reported physical and mental health status among cardiovascular patients.

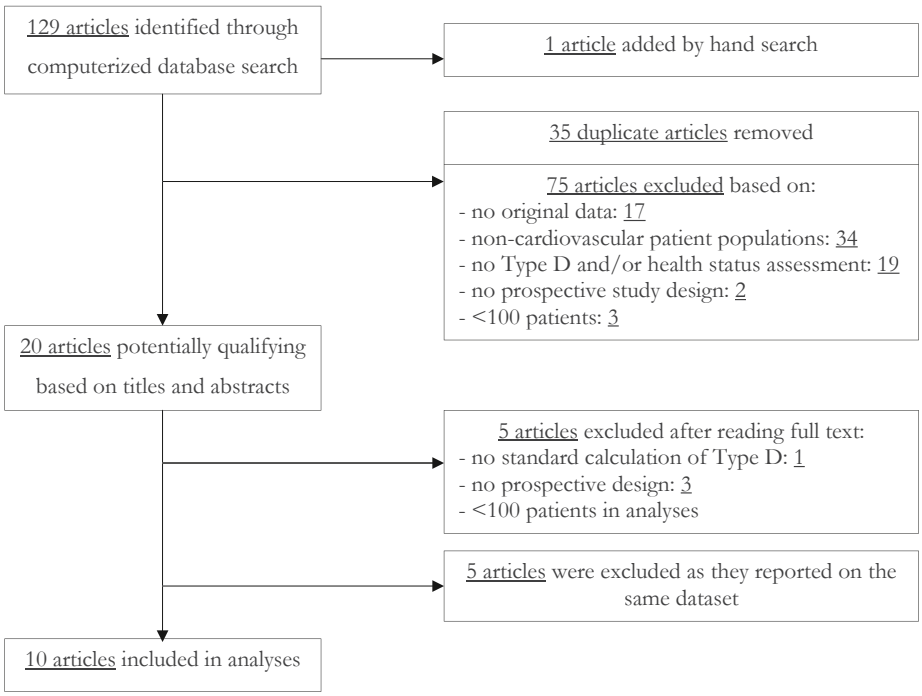
METHODS

Literature search and article selection

In a computerized search of the literature (Pubmed and PsychINFO for the period January 1995-May 2011), the following search terms were used: *Type D personality* in combination with *health status* or *quality of life*. Also, reference lists of included articles were checked by the first author (HV). The search was limited to original publications in peer-reviewed journals. Two independent raters (HV, JD) identified studies that: 1) were conducted in cardiovascular populations; 2) analyzed the association between Type D (determined by the standardized method)[18] and health status or health-related quality of life; 3) had a prospective design and 4) had a sample size of ≥100 patients.

Regarding multiple reports on the same dataset, only the article with the largest sample size was included in the meta-analyses. If necessary, corresponding authors were contacted with the request to provide additional information. A flow diagram of the literature search is shown in Figure 1.

Figure 1. Flowchart of the selection procedure



End points

The end point was health status or health-related quality of life, assessed with a validated and standardized instrument. We conducted separate meta-analyses for the association of Type D personality with physical and mental health status, respectively.

Quantitative Data Synthesis

Adjusted odds ratios (ORs) from the studies were pooled, using the program Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey). However, for one study adjusted ORs were not available,[19] so we converted the time-related data into simple 2 X 2 tables for which unadjusted ORs and 95% confidence intervals (CIs) were calculated. As we suspected a relatively large heterogeneity in results, we used the random effects method to generate a summary estimate of ORs and tested the amount of heterogeneity with the Q test of homogeneity and the I^2 test, which indicates the proportion of total variance explained by heterogeneity. The potential influence of baseline health status, follow-up length, health status assessment, research

group, and study sample were examined in secondary analyses. Differences in effect estimates between the subgroups were assessed by comparing the pooled effect estimates with Chi-square analyses by means of the logarithms of these estimates. To evaluate the presence of publication bias, funnel plots were constructed by plotting the effect measure against the inverse of its standard error. We used Egger's test of the intercept and the classic Fail-Safe N to test to estimate the severity of publication bias.

RESULTS

Of all identified studies, 10 met the selection criteria (Table 1). Authors of 7 of the included articles were contacted for additional information.[20-26]

Physical health status

All 10 studies were included in the meta-analysis on physical health status, comprising 3035 patients.[15,19-27] The mean follow-up period was 14.7 months, with follow-up periods ranging from 3 to 60 months. The pooled OR for the association of Type D personality with impaired physical health status was 1.94 (95% CI:1.49-2.52, p<.001) (Figure 2). There was no significant heterogeneity (Q=12.78, p=.17, I^2=29.59), so no further secondary analyses were conducted.

A funnel plot of the 10 studies did not suggest publication bias. Egger's test showed no significant asymmetry (p(one-tailed)=.13). The fail-safe N indicated that another 84 null-studies would be needed for the p-value to exceed .05.

Mental health status

Eight studies were included in the meta-analysis on mental health status, comprising 2213 patients.[19,21-27] The mean follow-up period was 6.9 months, with follow-up periods ranging from 3 to 24 months. The pooled OR for the association between Type D personality and impaired mental health status was 2.55 (95% CI:1.57-4.16, p<.001) (Figure 3). There was heterogeneity between studies (Q=21.91, p=.003, I^2=68.04) and subgroup analyses showed that the 4 studies controlling for baseline health status had a significantly smaller (p=.001) pooled OR (1.57, 95% CI:1.01-2.42; p=.04) compared to studies not controlling for baseline health status (OR=4.35, 95% CI:2.83-6.69; p<.001). There were no significant differences for follow-up period, health status assessment, research group, and study sample.

A funnel plot of the 8 studies did not suggest publication bias. Egger's test showed no significant asymmetry (p=.43). The fail-safe N indicated that another 88 null-studies would be needed for the p-value to exceed .05.

Table 1. Overview of studies included in the meta-analyses

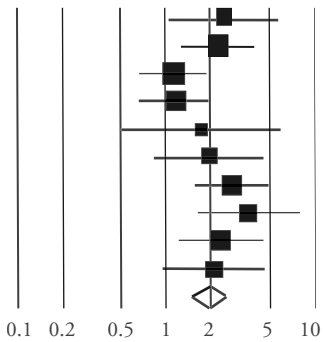
First author, year	N	Patient sample	Mean age Males	Type D (%)	Health status assessment	FU (months)	Covariates
Dannemann, 2010 (19)	126	CAD (CABG/ valve surgery)	67.0 yrs 75%	26%	SF-12	6	-
Denollet, 2000 (15)	319	CAD (cardiac rehab)	56.7 yrs 92%	31%	HCS	60	LVEF, exercise tolerance, thrombolysis, hypertension, hyperlipidemia, ACE-inhibitors, beta-blockers, aspirin, smoking age, gender anxiety, depression
Pedersen, 2007 (21)	692	CAD (PCI)	62.7 yrs 72%	28%	SF-36	12	cardiac history, recent event, multivessel disease, DM, hypertension, dyslipidemia, renal impairment, stent type, smoking age, gender baseline health status
Pelle, 2008 (24)	368	CAD (cardiac rehab)	58.1 yrs 79%	27%	SF-36	3	cardiac history, DM, COPD, renal insufficiency, smoking age, gender anxiety, depression, baseline health status

Skodova, 2011 (26)	106	CAD	57.4 yrs 85%	59%	SF-36	12-24	LVEF, type of intervention age, gender, education psychological well-being, vital exhaustion, baseline health status
Pedersen, 2010 (22)	251	CHF	71.9 yrs 47%	32%	MLWHFQ	9	NYHA class age, gender, marital status, education, employment status depression, baseline health status
Pelle, 2009 (25)	313	CHF	65.7 yrs 71%	22%	MLWHFQ	6	NYHA class, LVEF, etiology of CHF, time since diagnosis age, gender, marital status, education
Aquarius, 2007 (27)	203	PAD	64.5 yrs 64%	34%	RAND-36	12	ankle branchial index, absolute claudication distance age, gender
Mols, 2010 (20)	503	MI	60 yrs 77%	20%	SAQ	18	LVEF age, gender depression
Pedersen, 2007a (23)	154	ICD	58.5 yrs 81%	23%	SF-36	3	ICD indication, CRT, CHF, shocks, digoxin

ACE-inhibitor=angiotensin-converting enzyme inhibitor; CABG=coronary artery bypass graft surgery; CAD=coronary artery disease; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CRT=cardiac resynchronization therapy; DM=diabetes mellitus; HCS=Health Complaints Scale; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; MI=myocardial infarction; MLWHFQ=Minnesota Living with Heart Failure Questionnaire; NYHA=New York Heart Association; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; RAND-36=RAND 36-item Health Survey; SAQ=Seattle Angina Questionnaire; SF-12/36=12/36-item Short Form Health Survey.

Figure 2. Meta-analysis of the association between Type D and physical health status[a]

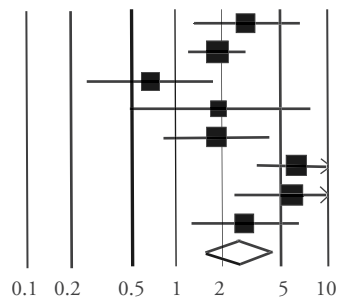
Study name	Odds ratio	Lower limit	Upper limit	z-value	*p*-value
Dannemann (2010)	2.423	1.032	5.690	2.032	0.042
Denollet (2000)	2.200	1.246	3.886	2.716	0.007
Pedersen (2007)	1.100	0.662	1.827	0.368	0.713
Pelle (2008)	1.153	0.655	2.029	0.494	0.621
Skodova (2011)	1.730	0.509	5.884	0.878	0.380
Pedersen (2010)	1.970	0.831	4.668	1.540	0.123
Pelle (2009)	2.760	1.551	4.912	3.451	0.001
Aquarius (2007)	3.650	1.670	7.979	3.245	0.001
Mols (2010)	2.344	1.198	4.586	2.488	0.013
Pedersen (2007a)	2.110	0.923	4.825	1.770	0.077
	1.941	1.494	2.522	4.966	0.000



[a] the bottom line shows the pooled results

Figure 3. Meta-analysis of the association between Type D and mental health status[a]

Study name	Odds ratio	Lower limit	Upper limit	z-value	*p*-value
Dannemann (2010)	2.906	1.285	6.571	2.563	0.010
Pedersen (2007)	1.870	1.192	2.934	2.723	0.006
Pelle (2008)	0.674	0.258	1.759	-0.806	0.420
Skodova (2011)	1.920	0.480	7.680	0.922	0.356
Pedersen (2010)	1.850	0.812	4.213	1.456	0.143
Pelle (2009)	6.180	3.394	11.253	5.956	0.000
Aquarius (2007)	5.970	2.426	14.689	3.890	0.000
Pedersen (2007a)	2.830	1.242	6.449	2.475	0.013
	2.553	1.567	4.158	3.765	0.000



[a] the bottom line shows the pooled results

DISCUSSION

This is the first meta-analysis evaluating the role of personality in explaining individual differences in health status reported by cardiovascular patients. Results showed that Type D personality is independently associated with 2-fold increased odds for impaired physical health status and 2.5-fold increased odds for impaired mental health status in various cardiovascular patient groups. After adjustment for baseline health status, the association of Type D with mental health status decreased but remained significant.

Assessment of patient reported health status is a key component of patient-centered clinical care,[4] as patients want to know how a treatment will affect their symptoms, function, and quality of life, particularly because some patients prefer a better health status over prolonged survival.[28] The incorporation of health status measures in clinical practice offers clinicians insight into their patient's physical and emotional needs and may be useful in clinical decision making.[4] To enhance patient-centered care, identification of factors that are associated with individual differences in patient reported health status is essential.[11] Knowing which factors are associated with negative patient reported outcomes may provide targets for improving health status and even prognosis, as patient reported health status has been shown to have incremental value over indicators of disease severity in predicting mortality and rehospitalisation.[5] Research has shown that the physician's evaluation of the patient's health and objective indicators of disease severity are only marginally associated with the health status as reported by patients.[7-9] The findings of the current meta-analyses are in line with previous studies emphasizing the importance of also taking into account important psychological factors, such as Type D personality.[12-14]

Personality is a relatively stable construct that refers to a person's 'normal baseline' or his/her general propensity to respond to stressful and life events,[16] while health status is a state-dependent outcome that will vary over time and according to the individual's personality disposition. As the current meta-analysis suggests, patients with a 'baseline' Type D personality are more prone to experience impaired health status. Yet their Type D personality traits persist following treatment that improves their health status,[24] in the same way that a compromised immune system makes a person more prone to get an infection but persists after the infection has been treated.[29] The stable adverse effect of Type D on health status is further emphasized by the finding that of the 6 studies in this meta-analysis that examined the Type D by time interaction effect,[19,21-24,27] only one found it to be significant.[21]

Type D personality has previously been associated with a poor cardiovascular prognosis[16] and a higher prevalence of cardiovascular risk factors.[30] The current results indicate that cardiovascular patients with a Type D personality are also more prone to report impaired physical and mental health status compared to their non-Type D counterparts. There are several potential pathways that could explain this relationship.

First, it has been argued that the cardiovascular effects of psychological factors,

such as Type D personality, could be confounded by disease severity.[31] However, studies in myocardial infarction and congestive heart failure patients have shown that Type D is not associated with markers of cardiac disease such as left ventricular ejection dysfunction,[32] multivessel disease,[32,33] or brain natriuretic peptide,[34] contradicting the argument that Type D patients are by definition more severely diseased. Second, the finding that Type D patients report poorer health status might be a result of their dysfunctional symptom and illness perceptions. Individuals with a Type D personality, characterized by high negative affectivity, may be more likely to perceive and attend to normal bodily sensations and to interpret them as painful or pathological.[35] Also, Type D patients tend to believe that their illness will have more serious consequences and that treatment will be less effective.[36] Third, the impaired health status of Type D patients may be the result of less adequate self-management behaviour. Type D has been associated with an unhealthy lifestyle (e.g. smoking, alcohol consumption, not exercising),[37] medication non-adherence,[38] and inadequate consultation behaviour.[25,39] Psychosocial and behavioural interventions aimed towards modifying the dysfunctional illness beliefs and health behaviours of Type D patients might reduce their levels of distress and improve their mental and physical health.[40]

Some limitations should be acknowledged. First, 8 of the 10 studies included in this meta-analysis stem from our own group and there is a need for more research by independent groups. Lately, the number of Type D studies from other research groups has increased rapidly. Except for one null finding,[26] these studies support the association between Type D personality and impaired health status.[19,41-46] However, most of these studies had a cross-sectional design[41,44,46] or a sample size <100 patients,[43,45] so only 2 studies from other research groups were included in the current meta-analyses.[19,26] Second, a limitation of meta-analytic research is the inevitability of combining data from studies with heterogeneous designs. There was no heterogeneity in study results for physical health status but studies that adjusted for baseline health status found a smaller association between Type D and impaired mental health status. This may be due to the fact that Type D exerts a stable, adverse effect on mental health across time and situations;[24] hence, adjusting for baseline mental health could lead to overcorrection.

In conclusion, the current findings emphasize that Type D personality may partly explain some of the individual differences in health status reported by cardiovascular patients, independent of indicators of disease severity and depression. Researchers and clinicians should take into account the patient's general propensity to psychological distress when seeking to identify patients at risk for poor health outcomes. This propensity to psychological distress can be reliably assessed with the 14-item Type D scale (DS14), which comprises little patient burden.[18] The findings of this meta-analysis indicate that the timely identification and treatment of high-risk patients with a Type D personality is warranted to improve individualized care.

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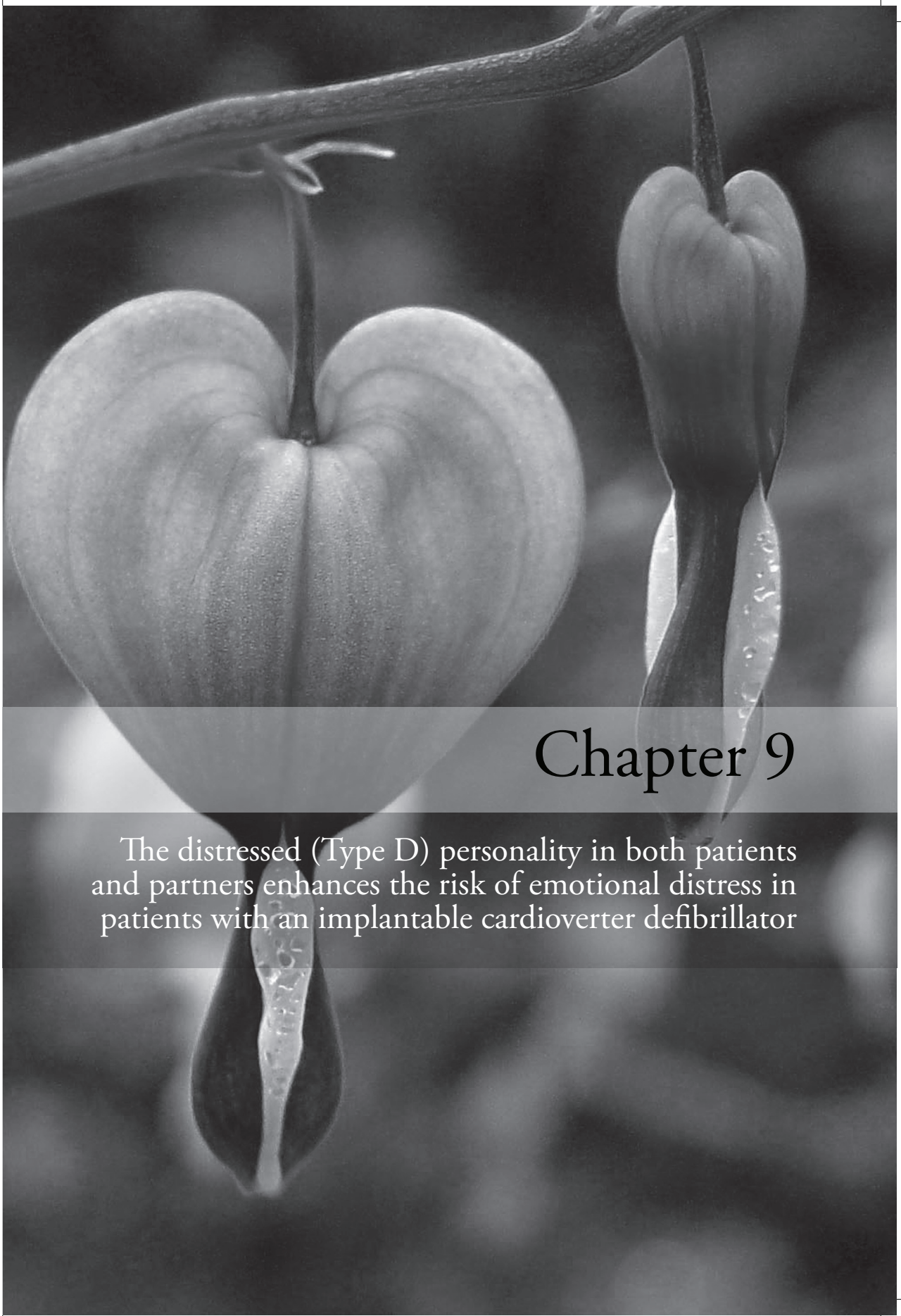


Chapter 9

The distressed (Type D) personality in both patients and partners enhances the risk of emotional distress in patients with an implantable cardioverter defibrillator

ABSTRACT

Background A subgroup of patients with an implantable cardioverter-defibrillator (ICD) experiences emotional distress. This may be related to partner factors. We examined the impact of the personality of the partner (i.e., the distressed (Type D) personality) in combination with that of the patient on anxiety and depression levels in ICD patients.

Methods Consecutively implanted ICD patients (N=281, 80.1% men, mean age=58.3±11.0) and their partners (*N*=281, 20.6% men, mean age=56.5±11.7) completed the Type D Scale at baseline; patients also completed the Hospital Anxiety and Depression Scale at baseline and 6 months post implantation.

Results ANOVA for repeated measures, using the Type D main effects and the interaction effect, showed that the interaction Type D patient by Type D partner was significant ($F_{1,277}$=7.0, p=.009) for depression as outcome, but not for anxiety ($F_{1,277}$=3.1, p=.08). Post-hoc comparisons revealed that Type D patients with a Type D partner (*n*=23/281; 8.2%) experienced the highest depression levels compared to other personality combinations (all ps<.05).

Conclusions ICD patients with a Type D personality report more depressive symptoms, but not anxiety, if the partner also has a Type D personality. This may be due to poor communication and lack of emotional support in the relationship. These results emphasize the importance of taking into account the psychological profile of the partner in the management and care of the ICD patient, and to direct behavioral support not only at the ICD patient but also at the partner.

van den Broek KC, Versteeg H, Erdman RAM, Pedersen SS. The distressed (Type D) personality in both patients and partners enhances the risk of emotional distress in patients with an implantable cardioverter defibrillator. J Affect Disord 2011; 130:447-453.

INTRODUCTION

The implantable cardioverter defibrillator (ICD) is implanted in patients who have experienced a sudden cardiac arrest (secondary prevention) and in patients who are at risk for a sudden cardiac arrest, due to a decreased ejection fraction (primary prevention).[1] The medical benefits of the ICD over pharmacological therapy are unequivocal in preventing sudden cardiac death in most patients,[2] but adaptation problems exist in 25% to 33% of ICD patients who experience increased emotional distress,[3,4] which in turn may trigger new life-threatening arrhythmias,[5,6] and influence survival.[7-9] These emotional problems may be more related to the psychological profile of the patient than to clinical factors, such as indication for the ICD, ICD shocks, or an ICD advisory.[3,4,10-12]

Distress levels in patients may also be related to partner factors. In a mixed sample of post myocardial infarction patients and ICD patients, patients with a Type D (distressed) personality without a partner showed higher distress levels than Type D patients with a partner.[13] Higher distress levels in cardiac patients have also been related to higher distress levels in their partners,[14] and research has shown that partner distress levels can be as high as distress levels in patients with an ICD.[15] In addition, lower survival rates were found in cardiac patients who reported low marital quality.[16] However, research has not focused on the influence of other partner characteristics, such as the personality of the partner, on patient distress.

The distressed (Type D) personality refers to the joint presence of two broad and normal personality traits, namely negative affectivity and social inhibition.[17] Persons with high levels of negative affectivity experience a broad range of negative emotions across time and situations. These persons generally have a gloomy view of themselves and the world. A high level of social inhibition refers to avoidance of social interactions, mainly because of fear of disapproval by others. Hence, Type D individuals are inclined to keep their negative feelings to themselves and not express them. Research, which has been performed primarily in cardiac populations, has shown that Type D patients are at increased risk for morbidity and mortality.[18] Specifically in ICD patients, Type D personality is associated with increased emotional distress,[4,13] impaired quality of life,[10] and also with new life-threatening arrhythmias[5] and mortality.[9] Little is known about the impact of both the patient and his/her partner having a Type D personality. This combination may incur the highest risk for distress because both individuals experience high levels of negative emotions, but at the same time they do not disclose their emotions, resulting in poor communication and lack of social support in the patient-partner dyad.

Hence, the objective of this prospective study was to examine the impact of concordant versus discordant personality types (i.e., Type D personality) of the patient and the partner on symptoms of depression and anxiety in patients with an ICD. We hypothesized that the personality of the partner would influence distress levels in the

patient, and that the highest distress levels would be found in patients whose partner also has a Type D personality.

METHOD

Study design and participants

The sample for this study comprised consecutive patients receiving an ICD implantation between August 2003 and December 2008 at the Erasmus Medical Center, Rotterdam, the Netherlands, and their partners. All patients and partners participated in the ongoing Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Exclusion criteria were a life expectancy of less than 1 year, on the waiting list for heart transplantation, a history of psychiatric illness other than affective/anxiety disorders (i.e., a mental disorder involving abnormal moods and emotions), or with insufficient knowledge of the Dutch language.

During clinical visits to the hospital, patients and their partners were asked to complete a set of standardized and validated psychological questionnaires at baseline (i.e., one day prior to ICD implantation) and at 6 month follow-up. Only patient and partner dyads with complete data were included in the statistical analyses.

The MIDAS study protocol was approved by the medical ethics committee of the Erasmus Medical Center. The study was conducted conform to the ethical tenets developed by the World Medical Association, as espoused in the Declaration of Helsinki. All patients provided written informed consent.

Measures

Demographic and clinical variables

Demographic and clinical variables were obtained at baseline from the patients' medical records and through purpose-designed questions. Demographic variables included gender, age, education (secondary school or less vs. high school/university), and working status. Clinical variables included indication for ICD implantation (primary vs. secondary prevention), cardiac resynchronization therapy (CRT), coronary artery disease (CAD) etiology, heart failure, diabetes mellitus, smoking, cardiac and psychotropic medication, and shocks (both appropriate and inappropriate) during the 6-month follow-up period.

Type D personality

At baseline, both patients and partners completed the 14-item Type D Scale (DS14) to assess Type D personality.[17] The DS14 consists of 2 subscales, negative affectivity (e.g., 'I often feel unhappy') and social inhibition (e.g., 'I am a closed kind of person'), each comprising 7 items. Items are answered on a 5-point Likert scale ranging from

0 (false) to 4 (true), with total scores ranging from 0 to 28 for both subscales. The patient had to complete at least 6 out of 7 items per subscale to be included in statistical analyses, with the 7th item being replaced by the mean of the other 6 scores. Patients scoring high on both subscales according to a standardized cut-off score ≥10 are classified as Type D.[18,19] The DS14 is a valid and reliable scale with Cronbach's alphas of .88 and .86 and a high test-retest reliability over a 3-month period of r=.72 and .82 for the negative affectivity and social inhibition subscales, respectively.[18] A study in post-myocardial infarction patients demonstrated that the DS14 is a stable personality measure over an 18-month period and that scores are not confounded by indicators of disease severity.[20]

Depression and Anxiety

Symptoms of depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire with a 7-item anxiety and 7-item depression subscale.[21] Items are scored on a 4-point Likert scale ranging from 0 to 3, with a score range of 0-21 for both subscales. Patients had to fill in at least 6/7 items to be included in statistical analyses, with mean imputation begin used for the missing 7th item. The Dutch version of the HADS has been shown to be valid and reliable, with Cronbach's alphas ranging from .71 to .86 for the depression subscale and from .80 to .84 for the anxiety subscale, and the test-retest reliability being .86 and .89, respectively.[22] Patients completed the HADS at baseline and 6 months follow-up.

Statistical analyses

To examine differences in baseline characteristics stratified by concordant and discordant Type D status of patients and their partners, we used the Chi-square test for discrete variables and analysis of variance (ANOVA), with post-hoc Bonferroni testing if applicable, for continuous variables.

The independent impact of Type D personality of the patient and partner on patients' depression and anxiety levels was examined by ANOVA for repeated measures with Type D personality of the patient, Type D personality of the partner, and their interaction as between-subject factors. When we found a significant three- or two-way interaction effect, we did not report on the main effects. Instead, we performed post hoc analyses with a Games-Howell (for unequal groups with unequal variances) or Hochberg T2 correction (for unequal groups with equal variances) to examine the differences between groups based on the combined Type D status of the patients and their partners. Also, paired-samples t tests were used to examine changes in depression and anxiety levels during follow-up. When we did not find a significant interaction effect, we reran the ANOVA without the interaction term.

Analysis of covariance (ANCOVA) for repeated measures was performed to adjust for the potential confounding effects of age, gender, education (secondary school or

less vs. high school/university), ICD indication (primary vs. secondary), CRT, CAD, heart failure, shocks (≥1), diabetes, psychotropic medication, and smoking.

All tests were two-tailed and $p<.05$ was used to indicate statistical significance. All data were analyzed using SPSS.17.0 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics for the total group and stratified by the personality of the patient and the partner

In total, 391 patients were approached, of which 281 could be included in the current analyses (see Figure 1 for a flow-chart of the sample selection). The mean age of the partners was 56.5±11.7 and 20.6% of partners were male. In total, 20 patients had received at least one ICD shock, with 5 patients receiving inappropriate shock(s) only, 14 patients appropriate shock(s) only, and 1 patient both.

Figure 1. Flowchart of the study

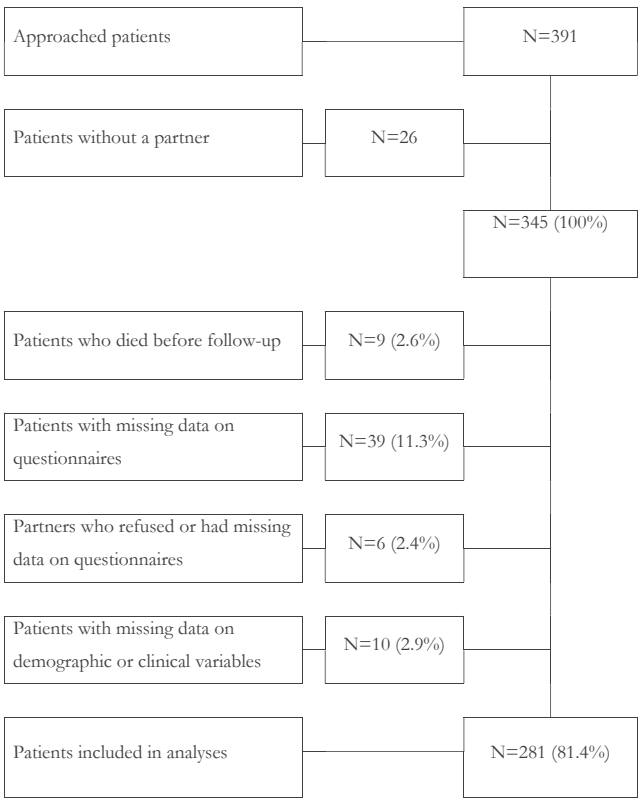


Table 1. Demographic and clinical characteristics of ICD patients stratified by Type D personality status of patient and partner

	Total *N* = 281	Non-TD patient Non-TD partner *n* = 172	Non-TD patient TD partner *n* = 51	TD patient Non-TD partner *n* = 35	TD patient TD partner *n* = 23	*p*
Demographics						
Age, mean (SD)	58.3 (11.0)	58.5 (10.9)	56.0 (12.1)	58.2 (9.6)	61.6 (10.7)	.23
Women	56 (19.9)	35 (20.3)	11 (21.6)	8 (22.9)	2 (8.7)	.55
≤Secondary school	160 (56.9)	97 (56.4)	30 (58.8)	20 (57.1)	13 (56.5)	.99
Currently employed	110 (39.1)	66 (38.4)	24 (47.1)	13 (37.1)	7 (30.4)	.54
Clinical factors						
Primary indication	184 (65.5)	112 (65.1)	31 (60.8)	24 (68.6)	17 (73.9)	.71
CRT	80 (28.5)	47 (27.3)	14 (27.5)	12 (34.3)	7 (30.4)	.86
CAD	161 (57.3)	99 (57.6)	25 (49.0)	19 (54.3)	18 (78.8)	.13
Heart failure	112 (39.9)	69 (40.1)	17 (33.3)	17 (48.6)	9 (39.1)	.57
Diabetes mellitus	38 (13.5)	20 (11.6)	9 (17.6)	5 (14.3)	4 (17.4)	.67
Smoking	28 (10.0)	18 (10.5)	4 (7.8)	3 (8.6)	3 (13.0)	.89
Medication						
Amiodarone	54 (19.2)	31 (18.0)	14 (27.5)	3 (8.6)	6 (26.1)	.13
Beta-blockers	222 (79.0)	134 (77.9)	43 (84.3)	28 (80.0)	17 (73.9)	.71
Digoxin	42 (14.9)	28 (16.3)	6 (11.8)	5 (14.3)	3 (13.0)	.87
Statins	165 (58.7)	97 (56.4)	28 (54.9)	21 (60.0)	19 (82.6)	.11
ACE-inhibitors	197 (70.1)	120 (69.8)	33 (64.7)	26 (74.3)	18 (78.3)	.63
Diuretics	153 (54.4)	93 (54.1)	25 (49.0)	23 (65.7)	12 (52.2)	.48
Psychotropic medication	47 (16.7)	26 (15.1)	6 (11.8)	10 (28.6)	5 (21.7)	.16

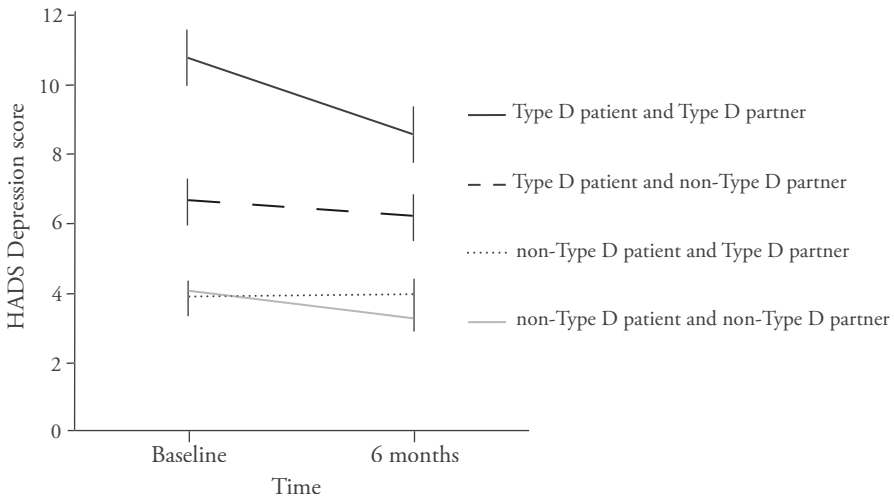
Results are presented as *n* (%), unless otherwise stated.
ACE=angiotensin converting enzyme; CAD=coronary artery disease; CRT=cardiac resynchronization therapy

Demographic and clinical characteristics for the total sample and stratified by 4 groups based on Type D status of patients and their partners are presented in Table 1. The first group comprised non-Type D patients with non-Type D partners (*n*=172, 61.2%), the second group non-Type D patients with Type D partners (*n*=51, 18.1%), the third group Type D patients with non-Type D partners (*n*=35, 12.5%) and the fourth group Type D patients with Type D partners (*n*=23, 8.2%). The 4 groups did not differ systematically on any of the demographic or clinical variables.

Depression

ANOVA for repeated measures showed that the three-way interaction time *by* Type D patient *by* Type D partner was significant ($F_{1,277}$=7.0, *p*=.009). Post hoc analyses were performed to examine the differences in depression levels between the 4 groups (Figure 2). Type D patients with Type D partners had significantly higher baseline levels of depression compared to the other 3 groups (all *p*s<.001). Type D patients with a non-Type D partner had significantly higher baseline depression levels compared to the non-Type D patients with (group 2: mean difference=2.7, *p*=.003) and without (group 1: mean difference=2.6, *p*=.001) a Type D partner. Baseline depression levels for non-Type D patients with and without a Type D partner were not significantly different (mean difference=-0.1, *p*=1.00). Paired samples *t* test showed that Type D patients with Type D partners and non-Type D patients with non-Type D partners experienced a significant decrease in depression levels during follow-up (mean difference=2.2, *p*=.007, and mean difference=0.8, *p*=.001, respectively), while the depression levels in the other 2 groups remained stable over time. At 6 months, there was only a borderline significant difference between depression levels of Type D patients with and without a Type D partner (mean difference=2.4, *p*=.06).

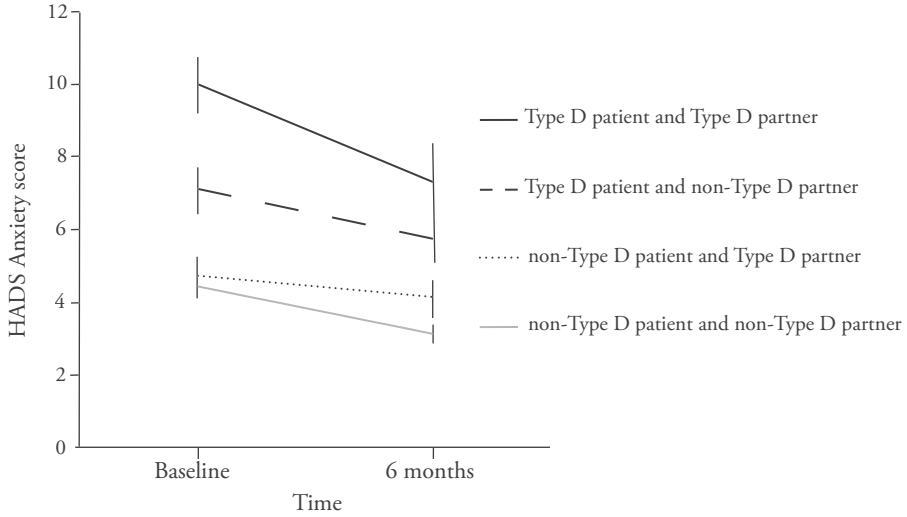
Figure 2. Mean depression levels in ICD patients stratified by Type D personality status of the patient and partner.



Anxiety

For anxiety, the time *by* Type D patient *by* Type D partner ($F_{1,277}$=3.1, p=.08) and the Type D patient *by* Type D partner interaction effects were not significant ($F_{1,277}$=2.6, p=.11). In the ANOVA without the interaction term, between-subjects effects for Type D patients ($F_{1,278}$=47.1, p<.001) and Type D partners ($F_{1,278}$=6.03, p=.02) were significant, indicating that the personality of the patient as well as the personality of the partner exerted a main influence on anxiety levels in the patient, with Type D patients and ICD patients with a Type D partner experiencing more anxiety than their counterparts (Figure 3). Anxiety levels declined significantly over the 6 month follow-up period ($F_{1,278}$=30.2, p<.001). This decline was not related to the specific personality type of patients nor partners ($F_{1,278}$=2.4, p=.12, and $F_{1,278}$=0.1, p=.75, respectively)

Figure 3. Mean anxiety levels in ICD patients stratified by Type D personality status of the patient and partner.



Multivariable analyses

Our main results did not change in adjusted analyses. Between-subjects effects of covariates showed that depression and anxiety levels were significantly different according to educational level ($F_{1,266}$=10.8, p=.001, and $F_{1,267}$=9.7, p=.002, respectively) and use of psychotropic medication ($F_{1,266}$=7.2, p=.007, and $F_{1,267}$=21.8, p<.001, respectively), with plots showing increased depression and anxiety levels in patients with lower education and in patients who use psychotropic medication. Shocks were neither significantly associated with depression nor anxiety levels ($F_{1,266}$=0.5, p=.48, and $F_{1,266}$=2.9, p=.09, respectively).

DISCUSSION

The findings of the current prospective study showed that not only the personality of the patient but also the combination with the partner's personality influenced depression levels in ICD patients, with Type D patients with a Type D partner experiencing the highest depression levels compared to other personality combinations. These patients also showed the largest decline in depression levels within 6 months post ICD implantation. There was no effect of patient/partner personality combination on anxiety, but both patient and partner personality types did exert a main effect on anxiety. This indicates that anxiety levels in Type D patients were higher than in non-Type D patients, but that it did not matter whether the partner was Type D or not, and also that anxiety levels were higher in ICD patients who have a Type D partner compared to ICD patients who did not have a Type D partner, but that the Type D status of the patient did not have additional value in these two groups.

Our finding that personality of the partner may influence distress levels in patients is in line with previous studies that also focused on the impact of partner factors on patient well being, although none of the previous studies specifically focused on the personality of the partner. For instance, Moser and Dracup reported that anxiety in spouses was positively related to emotional distress in cardiac patients.[23] Distress in partners has also been shown to influence survival in patients.[16] Finally, studies have shown that distress in partners of patients with a chronic disease is associated with poor health status in partners, through prolonged sympathetic activation and pronounced platelet activation and impaired endothelial function in partners.[24,25]

We do not know why Type D patients with a Type D partner are particularly vulnerable for developing depression, but can only speculate that it has to do with a number of factors that hamper communication in the patient-partner dyad. Generally, individuals with a Type D personality have a gloomy view of life and therefore, may view the ICD implantation as a negative event. Hence, both the Type D patient and the Type D partner may feel frustrated but at the same time are not willing to discuss the impact of living with an ICD on their lives. For this reason, it is unlikely that a Type D partner will ask the patient how he/she feels in order to avoid instilling conversations about fear. In addition, the patient is unlikely to be forthcoming with his/her uncertainties and worries. Due to misconstrued consideration and lack of communication, the Type D patient and the Type D partner may not be able to disclose their negative feelings within the boundaries of their relationship. Lack of support in combination with frustration may lead to depression, as lack of support is a known risk factor for increased emotional distress and adverse clinical events, such as mortality.[26]

We can only speculate why the combination of personalities seems to play no role in relation to anxiety. Perhaps it has to do with the type of emotion, with symptoms of anxiety and depression differing in their manifestations both at a behavioral and

physiological level. Anxiety symptoms are more difficult to hide and therefore are more visible than depressive symptoms, making it more evident that the patient is distressed.

Our longitudinal findings reflected a general decline in depression and anxiety levels within 6 months following ICD implantation, which has also been shown by others.[27] Type D patients with a non-Type D partner showed the largest decline in depression levels. This may reflect a real decline and not just regression to the mean, as the group non-Type D patients with non-Type D partners, who had the lowest depression levels, also showed a significant decline. The largest decline in the Type D patient-partner dyad may be attributed to Type D patients receiving extra attention from family and friends following the implantation, thereby encouraging them to express insecurities and concerns. Although Type Ds generally will refrain from talking about their negative feelings, this encouragement from significant others together with the fact that they have just undergone a major life event – the ICD implantation – may help them bridge their usual fear of talking about their emotions. In addition, given that these patients had the highest level of depression, there was more room for improvement in this group compared to the other groups.

In the current study, shocks were unrelated to depression and anxiety. Although ICD shocks tend to be viewed as the primary culprit if patients become anxious or experience a deterioration in quality of life,[28] a recent viewpoint indicates that evidence for a role of shocks on anxiety, depression, and quality of life in the general arrhythmia literature is mixed and perhaps more complex than previously assumed.[12] Due to the limited number of patients having received a shock during the follow-up period, it was not possible to differentiate appropriate from inappropriate shocks, although these may have a differential effect on emotional distress. Similarly, a focus on the number of shocks may be warranted, as the Canadian Implantable Defibrillator Study (CIDS) showed a dose-response relationship between shocks and quality of life,[29] although none of the other primary and secondary prevention trials confirmed this dose-response relationship.[12]

The limitations of the current study should be acknowledged. First, baseline assessment was one day before the implantation, which may have resulted in more increased anxiety and depression scores, due to anticipatory anxiety. For logistic reasons, it was not feasible to administer questionnaires prior to one day before implantation. Some patients know several weeks in advance that they will have an ICD implanted, while others receive an ICD acutely following a large infarction or a sudden cardiac rest. Given that all patients are admitted one day prior to implantation, this time point was chosen in order standardize the baseline assessment. Second, the follow-up period was limited to 6 months. Third, anxiety was measured using a general measure instead of a disease-specific measure. However, the HADS is less prone to confounding by disease severity, as the HADS does not include somatic

items.[21] Fourth, the prevalence of shocks was rather low, making it difficult to draw firm conclusions about the impact of shocks on distress levels. Finally, the group of Type D patients and Type D partners was rather small. Despite these limitations, to our knowledge, this is the largest study to date of patient and partner dyads with an ICD and the only study to have examined the influence of both the personality of the patient and the partner on patient distress levels.

Future studies are warranted to replicate the findings of our study, and also to examine the impact of the partner's personality in combination with the personality of the patient on patient morbidity and mortality, as several studies indicate that poor marital quality is related to mortality in patients.[16] In addition, research is warranted that examines the pathways through which combinations of personality in patients and partners may lead to increased emotional distress in patients, in order to be able to develop effective interventions.

These results emphasize the importance of taking into account the psychological profile of the partner in the management and care of the ICD patient. Currently, partners of patients with somatic disease tend to be neglected, as the main focus is on treatment of the ICD patient. Health care professionals should also be alert to the uncertainties and distress of partners, with the provision of adequate information and support being of primary importance. This can be achieved by inviting partners to participate in cardiac rehabilitation, as advocated by others,[30] which provides a forum for discussing emotional and practical aspects. Extra attention to Type D couples or couples with one Type D person may include encouragement to communicate with each other and to talk about uncertainties.

In conclusion, depressive symptoms were highest in ICD patients with a Type D personality if the partner also had a Type D personality, although this effect was not found with respect to anxiety. Future research is warranted to replicate these findings and investigate mechanisms and targets for intervention. Nevertheless, these results indicate that behavioral support should be directed not only at the ICD patient but also the partner.

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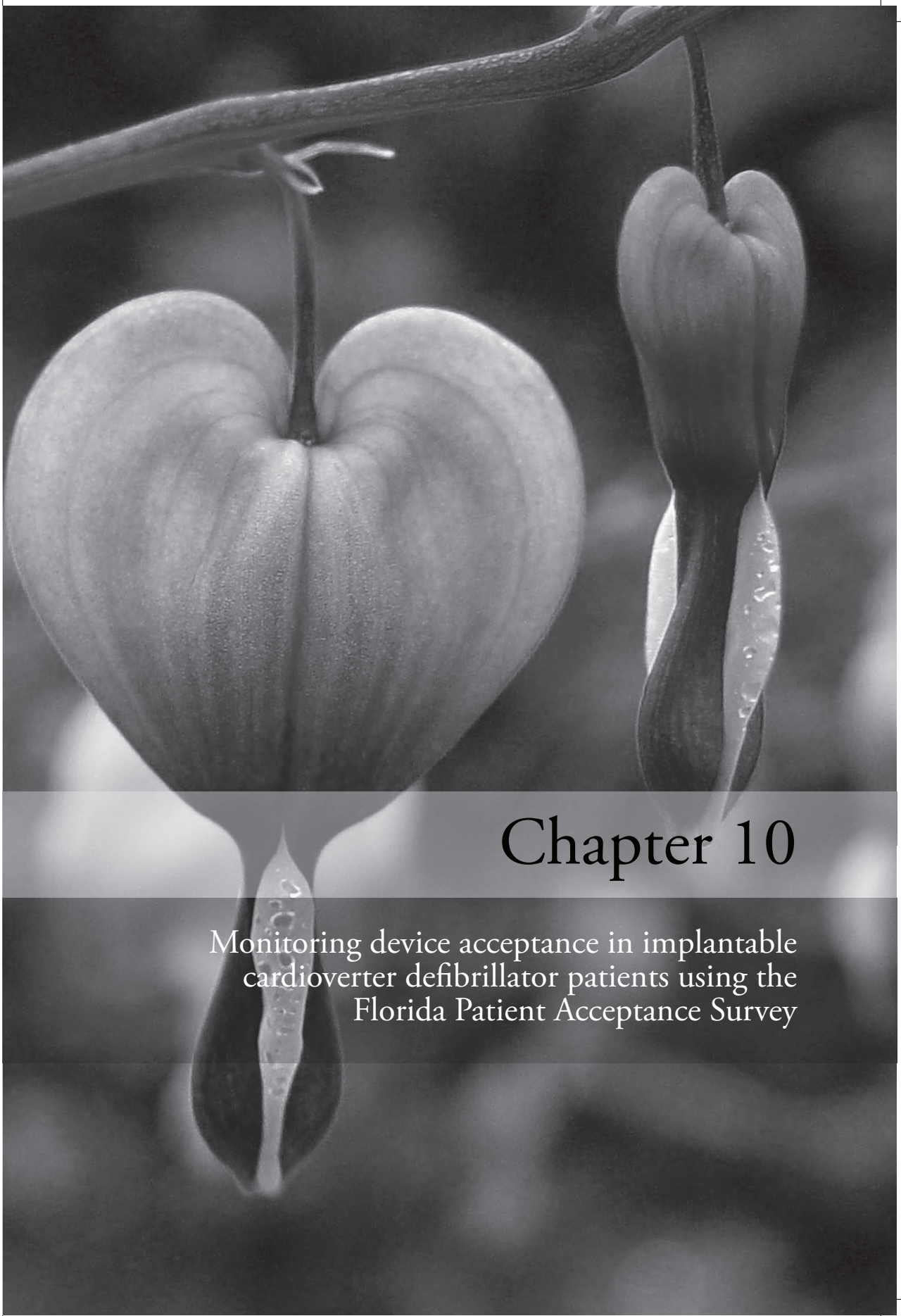

Chapter 10

Monitoring device acceptance in implantable cardioverter defibrillator patients using the Florida Patient Acceptance Survey

ABSTRACT

Objective To examine the validity and reliability of the Florida Patient Acceptance Scale (FPAS) and to identify correlates of patient device acceptance in a Dutch cohort of implantable cardioverter defibrillator (ICD) patients.

Methods Patients with a first-time ICD (*N*=272, mean age=59.2±11.9, 82% men) recruited from the Erasmus Medical Center, Rotterdam, or the Medisch Spectrum Twente, Enschede, the Netherlands completed the FPAS, the Type D Scale and the Hospital Anxiety and Depression Scale.

Results Exploratory and confirmatory factor analyses indicated that eliminating 3 items from the FPAS, leaving 12 items contributing to 3 factors is an equivalent to the original 4-factor version of the FPAS. The abbreviated FPAS had a high internal consistency both for the total scale and all subscales, with Cronbach's alphas ranging from .76 to .82. Anxiety (OR=9.75, 95% CI:2.38-39.87, *p*=.002), depression (OR=2.96, 95% CI:0.98-8.93, *p*=.05), and the distressed (Type D) personality (OR=5.04, 95% CI:1.50-16.92, *p*=.01), but not demographic and clinical factors including shocks, were significant independent correlates of poor device acceptance.

Conclusions A shortened 12-item, 3-factor version of the FPAS was shown to be a valid and internally consistent instrument to assess device acceptance in Dutch ICD patients. Psychological but not clinical factors were the primary correlates of device acceptance, which underlines the importance of taking into account the patient's psychological profile when seeking to identify patients at risk for adjustment difficulties after ICD implantation.

Versteeg H, Starrenburg A, Denollet J, van der Palen J, Sears SF, Pedersen SS. Monitoring device acceptance in implantable cardioverter defibrillator patients using the Florida Patient Acceptance Survey. *Submitted for publication.*

INTRODUCTION

Implantable cardioverter defibrillator (ICD) therapy is the treatment of choice for preventing sudden cardiac death in patients who have survived life-threatening arrhythmias (secondary prevention) or are at high risk for these arrhythmias (primary prevention).[1] Although the ICD is generally well tolerated and perceived as a potential lifesaver by the majority of patients,[2,3] a subset of patients suffer from emotional distress and poor quality of life after ICD implantation.[4,5]

Patient device acceptance is one of the factors that might be essential in identifying patients at risk for these adverse patient reported outcomes, as poor acceptance has been associated with psychological distress and a impaired quality of life in ICD patients.[2,6] Device acceptance refers to the psychological accommodation and understanding of the device and the derivation of benefit in terms of biopsychosocial functioning.[7] Previous studies suggest that device acceptance is not determined by ICD indication, ICD shocks, time since implantation, or device or lead advisory notices,[8-10] but rather by the presence of symptomatic heart failure and psychological factors, such as anxiety, depressive symptoms, and a distressed (Type D) personality.[2,6,11] The latter studies used the Florida Patient Acceptance Survey (FPAS), which is one of the few standardized and validated instruments available to measure ICD acceptance.[7]

The psychometric properties of the FPAS have previously been investigated in a North American and a Danish ICD patient sample.[7,11] Results showed that the FPAS has good validity and internal consistency. The objectives of the current study were to (1) examine the psychometric properties (i.e. factor structure, internal consistency, and divergent validity) of the FPAS, and 2) identify correlates of device acceptance, in 2 independent cohorts of Dutch ICD patients assessed at 10 days and 12 months post implantation, respectively.

METHODS

Study design and participants

The sample consisted of patients who had their first ICD implanted between August 2006 and January 2009 at the Erasmus Medical Center, Rotterdam, or the Medisch Spectrum Twente, Enschede, the Netherlands. Patients included in Rotterdam participated in the ongoing Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study (MIDAS). Patients included in Enschede participated in the Twente ICD Cohort Study (TICS). For both hospitals, exclusion criteria were age <18 years, significant cognitive impairments, a history of psychiatric illness other than affective/anxiety disorders, a life expectancy less than 1 year, and insufficient knowledge of the Dutch language. At 10 days (Rotterdam) or 12 months (Enschede) after implantation, patients were asked to complete a set of standardized and validated questionnaires. The study protocol was

approved by the Medical Ethics Committees of the participating hospitals. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

Measures

Demographic and clinical variables

Information on sex, age, etiology, ICD indication, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), diabetes mellitus, and cardiac medication use were retrieved from patients' medical records at time of implantation. Information on ICD shocks was obtained via device interrogation, while information on smoking was obtained by means of a purpose-designed question in the questionnaire.

Device acceptance

The FPAS is a measure of device acceptance consisting of 18 items.[7] Items are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree), with a high score indicating more acceptance. Of all items, 15 contribute to 4 subscales: (1) Return to Function (4 items); (2) Device-Related Distress (5 items); (3) Positive Appraisal (4items); (4) Body Image Concerns (2 items). The remaining 3 items are filler items. A total score based on the 15 items may also be calculated. Total and subscale scores are linearly converted into a score between 0 and 100. A high score on Return to Function and Positive Appraisal means better acceptance, while a high score on Device-Related Distress and Body Image Concerns represents less acceptance. The convergent and divergent validity of the FPAS are good, and the scale has been shown to be internally consistent, as indicated by Cronbach's alphas ranging from .74 to .83.[6,11] For the current study, the FPAS was translated from English into Dutch and back-translated according to standard procedures.

Type D personality

The distressed (Type D) personality was assessed with the 14-item Type D Scale (DS14).[12] Type D personality is defined by a general propensity to experience increased negative emotions paired with the non expression of these emotions in social interaction, due to fear of rejection or disapproval by others. The DS14 consists of 2 subscales, negative affectivity and social inhibition, each comprising 7 items. Items of the DS14 are answered on a 5-point Likert scale ranging from 0 (false) to 4 (true), with total scores for each subscale ranging from 0 to 28. Only patients scoring high on both subscales according to a standardized cut-off score ≥10 are classified as having a Type D personality.[12,13] The DS14 is a valid and reliable scale with Cronbach's alphas of .88 and .86 and a high test-retest reliability over a 3-month period of r=.72 and .82 for the negative affectivity and social inhibition subscales, respectively.[12] Type D

personality has previously been associated with increased distress, poor quality of life, and morbidity and mortality in ICD patients.[14-17] The DS14 was included to examine the divergent validity of FPAS and the role of personality as a correlate of patient device acceptance.

Anxiety and depressive symptoms

Anxiety and depressive symptoms were measured with the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report questionnaire.[18] The anxiety and depression subscales both consist of 7 items answered on a 4-point Likert scale ranging from 0 to 3, with a score range of 0-21. On both subscales, a cut-off ≥8 was used to indicate probable levels of clinical anxiety and depression, respectively. A review of 15 international studies using the HADS supports the use of this cut-off, as it yields an optimal balance between sensitivity and specificity.[19] The Dutch version of the HADS has been shown to be a valid and reliable instrument, with Cronbach's alphas ranging from .81 to .84 and from .71 to .86, and test-retest reliability over a mean 3-week period being r=.89 and .86 for the anxiety and depression subscales, respectively.[20] The HADS was used to evaluate the divergent validity of the FPAS and the association between anxiety and depressive symptoms and device acceptance.

Statistical analyses

Patient demographic and clinical baseline characteristics, stratified by center, were compared with the Chi-square test for discrete variables and the Student's t test for continuous variables. Principal component analysis (PCA) with varimax rotation was used to determine the factor structure of the FPAS. Prior to the PCA, Bartlett's test of sphericity and the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO-index) were examined to evaluate whether the data fulfilled the assumptions for carrying out a PCA. Eigenvalues and scree plots were used to determine the number of factors to extract. To validate the factor structure of the FPAS, we also performed confirmatory factor analysis using maximum likelihood estimation. Three overall goodness of fit indices (i.e., X^2, Root Mean Square Error of Approximation (RMSEA), and comparative fit index (CFI)) were calculated. A non-significant X^2 indicates a perfect fit, while a reasonably good fit between the model and the observed data is obtained when RMSEA is ≤.06 and CFI is ≥.95.[21] Cronbach's alpha and the mean inter-item correlation (MIIC) were calculated to examine the internal consistency of the FPAS subscales. MIIC was used in addition to Cronbach's alpha, since Cronbach's alpha is highly dependent on the number of items in each scale and hence prone to be inflated when the number of items is high. MIIC should fall in an optimal range between .20 and .50,[22] but should be no less than .15.[23]

Prior to multivariable logistic regression analysis to determine correlates of poor device acceptance, the FPAS total score was dichotomized, using the lowest tertile to

indicate poor device acceptance compared with the other two tertiles representing good device acceptance. Dichotomization has been advocated earlier to enhance clinical interpretability.[24] Results of the logistic regression analysis are presented as odds ratios (OR) with 95% confidence intervals (CI). All tests were two-tailed. A *p*-value of ≤.05 was used to indicate statistical significance. The analyses were performed using SPSS 17.0 and AMOS 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Table 1. Baseline characteristics for the total sample and stratified by center

	Total (*N*=272)	Rotterdam (*n*=136)	Enschede (*n*=136)	*p*
Demographics				
Age, mean (SD)	59.2 (11.9)	56.5 (11.8)	61.9 (11.4)	<.001***
Women	47 (17.3)	27 (19.9)	20 (14.7)	.26
Smoking	44 (16.2)	17 (12.5)	27 (19.9)	.12
Clinical factors				
Secondary prevention	76 (27.9)	34 (25.0)	42 (30.9)	.28
NYHA class III/IV	73 (26.8)	43 (31.6)	30 (22.1)	.08
LVEF <35%	193 (71.0)	101 (74.3)	92 (68.2)	.01*
Ischemic etiology	167 (61.4)	80 (58.5)	87 (64.0)	.38
Diabetes mellitus	41 (15.1)	17 (12.5)	24 (17.6)	.24
Medication				
Amiodarone	24 (8.8)	10 (7.4)	14 (10.3)	.39
Beta-blockers	220 (80.9)	105 (77.2)	115 (84.6)	.12
Digoxin	38 (14.0)	23 (16.9)	15 (11.0)	.16
Statins	174 (64.0)	80 (58.8)	94 (69.1)	.08
ACE-inhibitors	189 (69.5)	92 (67.6)	97 (71.3)	.51
Diuretics	156 (57.4)	66 (48.5)	90 (66.2)	.003**

Results are presented as *n* (%), unless otherwise stated.
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$
ACE= angiotensin converting enzyme; NYHA=New York Heart Association functional class; LVEF=left ventricular ejection fraction

Baseline characteristics, stratified by center, are displayed in Table 1. Patients included in Enschede were on average older (61.9 *versus* 56.5 years, $p<.001$), more likely to use diuretics (66.2% *versus* 48.5%, $p=.003$), and less likely to have a LVEF of <35% (68.3% *versus* 74.3, $p=.01$) at time of implantation compared with patients included in Rotterdam. There were no other significant differences in baseline characteristics between the two cohorts. Of note, there were no significant differences in baseline characteristics of patients with poor *versus* good device acceptance (results not shown).

In total, 25 patients (9.2%) had received (in)appropriate ICD shock(s) during follow-up, 23 of them belonged to the Enschede cohort (assessed at 12 months post implantation). Only 2 patients in the Rotterdam cohort (assessed at 10 days) had experienced an ICD shock.

Factor structure of the FPAS

Factor analysis was performed to examine the structural validity of the FPAS. The KMO-index (.81) and Bartlett's test of sphericity ($p<.001$) indicated that the data fulfilled the assumptions for carrying out a factor analysis. The eigenvalues >1 criterion confirmed the 4-factor structure of the FPAS (Table 2a). The 4 factors accounted for 64.4% of the variance (factor 1 (Device-Related Distress)=30.5%, factor 2 (Positive Appraisal)=13.8%, factor 3 (Return to Function)=12.7%, factor 4 (Body Image Concerns)=7.4%). However, the scree plot indicated a marked "elbow" that inflected after the 3rd factor. Also, the factor loading for item 12 on its supposed factor (i.e., Device-Related Distress) was low (.03), with this item loading higher on factor 4 (i.e., Body Image Concerns; factor loading=.68). Factor 4 had an eigenvalue of 1.12 and explained only 7.4% of the variance in device acceptance.

Hence, we reran the factor analysis with 12 items, excluding the 3 items loading on factor 4 (i.e., items 12, 14, and 15). This yielded a 3-factor structure (Table 2b), with the 3 factors accounting for 63.6% of the variance (factor 1=34.9%, factor 2=16.9%, factor 3=11.8%) and all items loading on their expected factors. To verify our results, we performed confirmatory factor analyses with 15 items (4 factors) and 12 items (3 factors), respectively. The X^2-test was statistically significant for both models ($X^2_{84}=199.0$, $p<.001$, and $X^2_{51}=99.5$, $p<.001$, respectively), indicating that both models do not fit the data perfectly. However, the X^2 difference test was significant ($X^2_{diff,33}=99.44$, $p<.05$), which suggests that the 3-factor model provides a significantly better fit to the data than the 4-factor model. Also, the two other goodness of fit indices slightly favored the 3-factor model over the 4-factor model (RMSEA=.06, $p=.18$ *versus* RMSEA=.07, $p=.004$, and CFI=.96 *versus* CFI=.92, respectively).

Table 2a. Structural validity and internal consistency of the original Dutch FPAS (15 items, 4 factors)

FPAS items	I	II	III	IV	Internal consistency
Device related distress					
1 Thinking about the device makes me depressed.	**0.82**	-0.19	0.16	0.01	0.59
2 When I think about the device, I avoid doing things I enjoy.	**0.80**	-0.09	0.29	0.10	0.66
3 I avoid my usual activities because I feel disfigured by the device.	**0.70**	-0.11	0.06	0.32	0.59
4 It is hard for me to function without thinking about my device.	**0.74**	-0.10	0.16	0.21	0.62
12 I am careful when hugging and kissing my loved ones.	**0.03**	-0.10	0.11	0.68	0.23
Eigenvalue = 4.58				α = 0.75, MIIC = 0.40	
Positive appraisal					
5 My device was my best treatment option.	-0.09	**0.66**	-0.08	-0.07	0.44
7 I am safer from harm because of my device.	-0.08	**0.84**	-0.12	-0.04	0.56
8 The positive benefits of this device outweigh the negatives.	-0.09	**0.81**	-0.05	-0.01	0.58
10 I would receive this device again.	-0.16	**0.77**	-0.06	-0.14	0.66
Eigenvalue = 2.06				α = 0.76, MIIC = 0.44	
Return to function					
6 I am confident about my ability to return to work if I want to	-0.01	0.22	**-0.66**	0.17	0.48
13 I have returned to a full life.	-0.20	0.24	**-0.70**	-0.07	0.70
17 I am not able to do things for my family the way I used to.	0.15	0.10	**0.80**	0.11	0.64
18 I am concerned about resuming my daily physical activities.	0.31	-0.02	**0.78**	0.14	0.64
Eigenvalue = 1.91				α = 0.80, MIIC = 0.50	
Body image concerns					
14 I feel that others see me as disfigured by my device.	0.19	-0.03	-0.01	**0.85**	0.69
15 I feel less attractive because of my device.	0.28	-0.10	-0.02	**0.79**	0.69
Eigenvalue = 1.12				α = 0.82, MIIC = 0.69	

Table 2b. Structural validity and internal consistency of the alternative Dutch FPAS (12 items, 3 factors)

FPAS items	I	II	III	Internal consistency
Device related distress				
1 Thinking about the device makes me depressed.	**0.77**	-0.19	0.17	0.68
2 When I think about the device, I avoid doing things I enjoy.	**0.81**	-0.09	0.28	0.72
3 I avoid my usual activities because I feel disfigured by the device.	**0.77**	-0.12	0.04	0.59
4 It is hard for me to function without thinking about my device.	**0.77**	-0.10	0.15	0.63
Eigenvalue = 4.19			α = 0.82, MIIC = 0.54	
Positive appraisal				
5 My device was my best treatment option.	-0.09	**0.67**	-0.09	0.44
7 I am safer from harm because of my device.	-0.08	**0.84**	-0.12	0.56
8 The positive benefits of this device outweigh the negatives.	-0.08	**0.81**	-0.06	0.58
10 I would receive this device again.	-0.22	**0.77**	-0.03	0.66
Eigenvalue = 2.03			α = 0.76, MIIC = 0.44	
Return to function				
6 I am confident about my ability to return to work if I want to	0.06	0.22	**-0.70**	0.48
13 I have returned to a full life.	-0.23	0.23	**-0.69**	0.70
17 I am not able to do things for my family the way I used to.	0.20	0.10	**0.78**	0.64
18 I am concerned about resuming my daily physical activities.	0.36	-0.01	**0.76**	0.64
Eigenvalue = 1.42			α = 0.80, MIIC = 0.50	

Internal consistency

The internal consistency of the 4 subscales (Device-Related Distress=.75; Positive Appraisal=.76; Return to Function=.80; Body Image Concerns=.82) and the total scale (.82), as measured by Cronbach's alpha, was acceptable (Table 2a). MIICs for 3 of the 4 subscales (Device-Related Distress=.40; Positive Appraisal=.44; Return to Function=.50) and the total scale (.25) were also within the optimal range of .20-.50, except for the MIIC for Body Image Concerns (.69). After excluding items 12, 14 and 15 (Table 2b), the internal consistency of the Device-Related Distress subscale increased (.82), but the MIIC for this subscale fell just outside the optimal range (.54). For the total scale, the internal consistency remained stable (.82) and the MIIC stayed within the optimal range (.28).

Of note, analyses for the two cohorts separately did not yield significantly different results concerning the factor structure and internal consistency of the FPAS. However, as the results concerning the divergent validity and correlates of the FPAS did differ between the two cohorts, these results will be presented separately in the subsequent sections.

In both cohorts, the FPAS, DS14 and HADS were completed at the same point in time (i.e., for the Rotterdam cohort all at 10 days and for the Enschede cohort all at 12 months post implantation), so the results are cross-sectional. Also, since the 12-item version of the FPAS seemed to be a better measure psychometrically, this version will be used from here on for all analyses. Mean scores and corresponding standard deviations at item level and for the subscales, and the scoring algorithm for the 12-item version are displayed in Appendix I.

Divergent validity

The correlation matrix on scale scores between FPAS, DS14, and HADS are shown in Table 3, stratified by center.

In the Rotterdam cohort (10 days post implantation), the FPAS Positive Appraisal subscale did not significantly correlate with the Negative Affectivity subscale of the DS14. For the other subscales and total score, the overlap between the FPAS and Negative Affectivity in terms of shared variance ranged from 14% to 19%. The FPAS Return to Function subscale did not significantly overlap with the DS14 Social Inhibition subscale, for the other (sub)scales the shared variance ranged from 3% to 7%. The overlap between the FPAS and HADS Anxiety ranged from 19% to 28%, but Anxiety was not significantly correlated with FPAS Positive Appraisal. The shared variance between the FPAS and HADS Depression ranged from 4% to 34%.

In the Enschede cohort (12 months post implantation), the FPAS Positive Appraisal subscale also did not significantly overlap with the DS14 Negative Affectivity subscale. For the other FPAS (sub)scales, the overlap with Negative Affectivity ranged from 3% to 8%. None of the FPAS (sub)scales correlated with the Social Inhibition

Table 3. Correlation matrix on (sub)scale scores (FPAS, DS14, HADS), stratified by center

	1	2	3	4	5	6	7	8
1 FPAS: Return to function	-	.42***	.22**	.79***	-.38***	-.17	-.44***	-.57***
2 FPAS: Device-related distress	.44***	-	.33***	.79***	-.43***	-.23**	-.58***	-.50***
3 FPAS: Positive appraisal	.25**	.31***	-	.63***	-.13	-.18*	-.12	-.20*
4 FPAS: Total (12 items)	.79***	.74***	.71***	-	-.44***	-.26**	-.53***	-.59***
5 DS14: Negative affectivity	-.18*	-.29**	.03	-.18*	-	.37***	.59***	.64***
6 DS14: Social inhibition	-.10	-.19*	-.05	-.14	.47***	.-	.13	.23**
7 HADS: Anxiety symptoms	-.45***	-.56***	-.20**	-.53***	.52***	.20*	-	.76***
8 HADS: Depressive symptoms	-.51***	-.38***	-.22*	-.50***	.46***	.34*	.67***	-

Above the diagonal = Rotterdam (10 days post implantation; dark grey); below the diagonal = Enschede (12 months post implantation; light grey).
All psychological factors are assessed at the same time as the FPAS.
*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$
DS14=14-item Type D scale; FPAS=Florida Patient Acceptance Survey; HADS=Hospital Anxiety and Depression Scale.

subscale of the DS14, except for Device-Related distress (4%). The overlap between the FPAS (sub)scales and HADS Anxiety and Depression ranged from 5% to 31% and from 4% to 26%, respectively.

Despite some overlap between the FPAS and the other psychological measures, in particular with anxiety and depression, these findings suggest that the FPAS measures a construct that is conceptually different from that of personality factors and mood states.

Correlates of poor device acceptance

Overall, both patient cohorts reported a positive appraisal of the device, with the mean FPAS total score (12 items) being high at 10 days and 12 months post implantation (71.8±14.9 and 73.8±16.0, respectively). Correlates of poor device acceptance, i.e. the lowest tertile on the FPAS total scale (score≤64.5), are shown in Table 4. For the Rotterdam cohort assessed at 10 days post implantation, Type D personality and high depression were independently associated with poorer acceptance of the ICD (OR=5.04, 95% CI:1.50-16.92, *p*=.01 and OR=4.40, 95% CI:1.04-18.65, *p*=.05, respectively). Of note, as only 2 patients (1.5%) had received an ICD shock during the 10 days follow-up, ICD shocks were not included as a covariate in the analysis for this cohort.

In the Enschede cohort assessed at 12 months post implantation, high anxiety (OR=9.75, 95% CI:2.38-39.87, *p*=.002) and depression (OR=2.96, 95% CI:0.98-8.93, *p*=.05), but not Type D personality (OR=0.71, 95% CI:0.22-2.33, *p*=.58), were significant associates of poor device acceptance. None of the demographic or clinical factors were associated with device acceptance.

DISCUSSION

The current study examined the psychometric properties and correlates of the FPAS, a disease-specific questionnaire to assess patient device acceptance, in two cohorts of Dutch ICD patients assessed at 10 days and 12 months post implantation, respectively. Results indicated that eliminating 3 items from the FPAS, leaving 12 items contributing to 3 factors (i.e., Return to Function, Device-Related Distress, and Positive Appraisal) is a psychometrically sound alternative to the original 15-item, 4-factor version of the FPAS, with validity and internal consistency preserved. Also, our results confirmed that the FPAS measures a construct that is conceptually different from that of mood states and personality, despite some overlap in particular with measures of anxiety and depression. Correlates of device acceptance included anxiety, depression, and Type D personality. Demographic and clinical factors, including ICD shocks, indication, and symptomatic heart failure were not associated with device acceptance.

Table 4. Correlates of poor device acceptance, stratified by center[a]

	Rotterdam (10 days)			Enschede (12 months)		
	OR	**[95% CI]**	***p***	**OR**	**[95% CI]**	***p***
Psychological factors[b]						
Type D personality	5.04	1.50-16.92	.01**	0.71	0.22-2.33	.58
Anxiety	2.46	0.49-12.45	.28	9.75	2.38-39.87	.002**
Depression	4.40	1.04-18.65	.05*	2.96	0.98-8.93	.05*
Demographic factors						
Age	1.03	0.98-1.09	.22	1.00	0.98-1.05	.93
Female gender	1.68	0.45-6.22	.44	0.78	0.19-3.15	.73
Smoking	0.59	0.12-2.87	.51	0.96	0.31-2.99	.94
Clinical factors						
Ischemic etiology	0.77	0.23-2.54	.67	0.97	0.35-2.85	.99
NYHA class III/IV	2.36	0.84-6.68	.10	0.64	0.20-2.06	.45
LVEF <35%	1.35	0.32-5.71	.69	1.33	0.41-4.32	.64
Secondary prevention	0.32	0.08-1.32	.11	1.48	0.53-4.19	.46
ICD shock	-	-	-	0.61	0.17-2.26	.46
Diabetes mellitus	0.77	0.16-3.83	.75	1.48	0.47-4.64	.50

Multivariable logistic regression analyses

[a] All factors, except age, were entered as dichotomous variables.

[b] All psychological factors are assessed at the same time as the FPAS.

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$

NYHA=New York Heart Association functional class; LVEF=left ventricular ejection fraction.

The current study confirms that the FPAS is a valid and internally consistent measure of device acceptance, as previously shown in North American and Danish cohorts,[7,11] indicating that the FPAS may be used to assess device acceptance beyond the North American context. Also, the factor structure and internal consistency of the FPAS were confirmed in both of our patient cohorts, assessed at 10 days and 12 months post implantation, indicating that it is robust over time. However, the results are on par with those of Pedersen and colleagues,[11] who also found that FPAS item 12 (i.e., 'I am careful when hugging and kissing my loved ones') was problematic in the Danish context, as it loaded poorly on the expected factor and had a much higher loading on the Body Image Concerns factor. This suggests that this item is culturally sensitive and if kept in the FPAS it needs to be rephrased. Also, in both the previous Danish study and the current Dutch study, the Body Image Concerns

factor explained just a small part of the variance in device acceptance (i.e., 6% and 7%, respectively), which might be due to this subscale only containing 2 items that may be not well formulated. Alternatively, these findings may be explained by the fact that in the current and in the Danish study the percentage of women was lower than in the North American study (17% *versus* 37%) and women may have more concerns about their body image than men.[25] However, a recent study has shown no gender differences in ICD acceptance, including body image concerns.[26]

Anxiety, depression, and Type D personality, and not demographic and clinical factors, were associated with poor device acceptance in adjusted analyses. These findings are in line with previous studies suggesting that the psychological profile of the patient is an equally and sometimes more important determinant of device acceptance and other patient reported outcomes than disease severity and shocks.[2,6,9,11,14,27] Hence, an expansion of the focus beyond shocks to also include psychological determinants is essential to identify patients at high risk for adjustment difficulties after device implantation.[28] Most studies, including our study, however, indicate that ICD patients generally view their device positively and experience low levels of device-related distress, even after being subjected to shock(s) or a device advisory notice.[3,8-10] The FPAS may be especially useful for examining the normative processes of adjustment to ICD therapy as it does not focus on maladjustment or psychopathology.[14] Hence, the FPAS is applicable to all patients. In addition, the FPAS has been shown to detect changes in psychological well being following psychosocial intervention,[29] suggesting that it is a sufficiently sensitive measure to tap changes in outcome, if present, following an intervention .

Previously, poor device acceptance has been associated with more emotional distress and impaired quality of life.[2,6] Hence, the FPAS could be used to identify patients at risk for poor patient reported outcomes who need adjunctive treatment. Psychosocial intervention, in particular cognitive-behavioral therapy and patient education, has been shown to have beneficial effects on device acceptance, quality of life and psychological distress levels in ICD patients.[29,30]

The limitations of the present study must be acknowledged. First, the study design was cross-sectional, and therefore, it is not possible to infer cause and effect. A future prospective study is warranted to determine whether psychological distress is a precursor of poor ICD acceptance or vice versa. Second, psychological variables were only assessed by means of self-report rather than interviews. However, all questionnaires were standardized and validated. Strengths of the current study were its relatively large sample size, the comparison of two independent ICD patient cohorts assessed at a different times post implantation, and the inclusion of information on disease severity, i.e. LVEF and NYHA functional class, in adjusted analyses.

In conclusion, the present study shows that the FPAS is a valid and internally consistent measure of patient device acceptance. Based on previous Danish findings and findings of the current study, we would suggest that the FPAS be shortened to a 12-item version assessing 3 factors. Abbreviation of the FPAS from the original 18 items to 12 items also makes it more suitable to use in research and clinical practice due to its brevity. However, until the findings of these two studies are confirmed in ICD cohorts in other countries, both the 12-item and the 18-item version of the FPAS could be used. The present and previous findings indicate that a small subgroup of patients experience difficulties with adjustment following ICD implantation, and that this likely is attributable not only to the severity of their disease and shocks but also to their psychological profile. The FPAS is a useful tool in research and clinical practice to examine the process of device adjustment and to identify patients at high risk for psychological difficulties after ICD implantation. Future intervention studies with a prospective design are warranted to examine how device acceptance can be augmented and the implications for well being and health outcomes of ICD patients.

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Appendix I. Means and standard deviations for the alternative Dutch FPAS (12 items, 3 factors, *N*=272)[a]

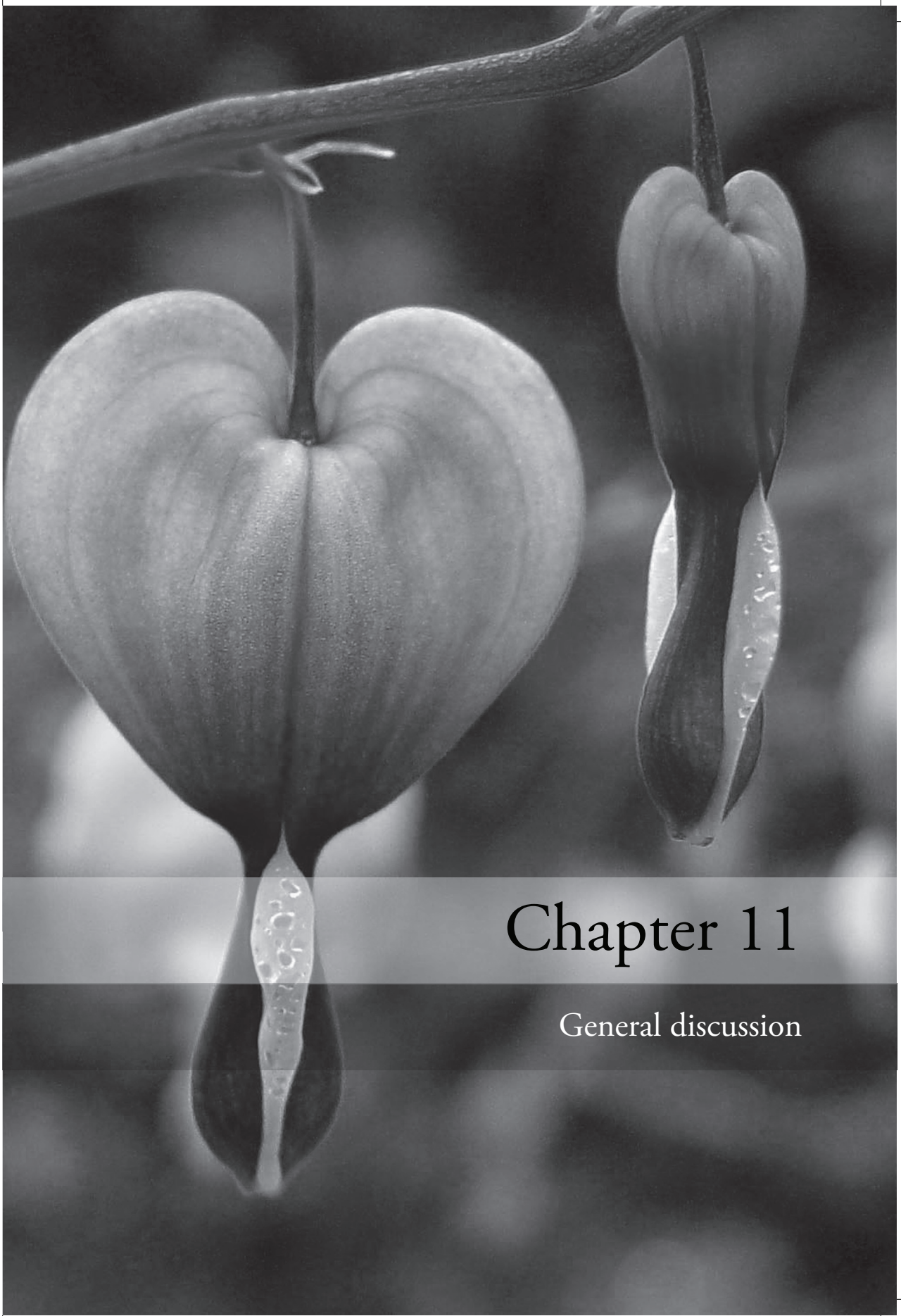
FPAS items	Original item no	Raw score[1]	Linearly converted score[2]
Device related distress		16.98 (3.05)	81.11 (19.09)
1 Thinking about the device makes me depressed.	1	1.99 (1.08)	
2 When I think about the device, I avoid doing things I enjoy.	2	1.82 (0.97)	
3 I avoid my usual activities because I feel disfigured by the device.	3	1.45 (0.76)	
4 It is hard for me to function without thinking about my device.	4	1.76 (0.95)	
Positive appraisal		16.12 (3.16)	75.74 (19.78)
5 My device was my best treatment option.	5	4.06 (1.01)	
6 I am safer from harm because of my device.	7	3.98 (1.03)	
7 The positive benefits of this device outweigh the negatives.	8	3.97 (1.09)	
8 I would receive this device again.	10	4.11 (0.90)	
Return to function		13.86 (3.78)	61.65 (23.62)
9 I am confident about my ability to return to work if I want to	6	3.36 (1.33)	
10 I have returned to a full life.	13	3.59 (1.14)	
11 I am not able to do things for my family the way I used to.	17	2.71 (1.28)	
12 I am concerned about resuming my daily physical activities.	18	2.38 (1.21)	
Total		49.96 (7.43)	72.83 (15.49)

[a] Results are presented as mean (SD)

[1] Raw scores: Device related distress=item 1r + item 2r + item 3r + item 4r; Positive appraisal=item 5 + item 6 + item 7 + item 8; Return to function=item 9 + item 10 + item 11r + item 12r; Total score=item 1r + item 2r + item 3r + item 4r + item 5 + item 6 + item 7 + item 8 + item 9 + item 10 + item 11r + item 12r

[r] Use reversed item score

[2] Linearly converted scores: Subscale scores=((raw subscale score – 4)/16*100); Total score=((raw total score-12)/48)*100.



Chapter 11

General discussion

Cardiovascular implantable electronic device therapy represents state-of-the art medical technology that has become the treatment of choice to improve prognosis in subgroups of patients with heart disease. Particularly, the implantable cardioverter defibrillator (ICD) and the biventricular pacemaker providing cardiac resynchronization therapy (CRT) used either alone or in combination (i.e., CRT-D) are now implemented on a large scale with their indications also likely to expand in the future.[1] The implicit assumption in the field is that any new and innovative technology that decreases morbidity and enhances survival must also be good for patients, with equal gains in well being and quality of life for all patients. Hence, inclusion of the patient perspective by means of assessing patient reported outcomes is currently not part of standard clinical research and practice when evaluating treatment effects of new innovations in the field. This dissertation focused on patient reported outcomes following ICD/CRT(-D) implantation and examined the role of disease- and device-related factors versus psychological factors in explaining individual patient differences in these outcomes. Findings from studies on a variety of ICD and CRT(-D) patient samples recruited from multiple national and international centers were presented. In the current chapter, these findings are discussed and their implications for clinical practice and future research are outlined.

DISCREPANCY BETWEEN THE PHYSICIAN AND THE PATIENT PERSPECTIVE

From the patient perspective, an important target of treatment is the relief of symptoms, reduction in functional limitations and improvement in quality of life.[2,3] In clinical practice, the physician's interpretation of the presence and severity of symptoms and limitations in patients with congestive heart failure (CHF) is often classified according to the New York Heart Association (NYHA) functional classification system. Besides improvement in echocardiographic and hemodynamic parameters, an improvement in ≥1 NYHA functional class is one of the most frequently used criteria to define response to CHF treatment (e.g., CRT) in clinical research and practice.[4,5] However, the existing CHF literature and clinical case reports indicate that there is a poor relationship between the traditional physician rated indicators of CHF severity, including NYHA functional class and echocardiographic parameters, and patients' own perceptions of health (*Chapter 2*).[6-9] This discrepancy was emphasized by results presented in the current dissertation showing that most of the variation in patient reported health status changes following CRT implantation could not be explained by NYHA functional class at the time of implantation (*Chapter 3*), and that clinically relevant improvements in patient rated health status occurred in the absence of improvement in NYHA functional class (*Chapter 4*). These findings underline that NYHA functional class should not be used as the sole outcome measure to determine improvements in symptoms, functional status, and quality of life after

CRT implantation, as it may not be sufficiently sensitive to tap changes perceived by patients. In addition, the NYHA functional classification system has been criticized for having poor intra- and inter-rater reliability and for primarily being a measure of general functional status.[10,11] However, CHF patients not only experience functional losses but also a variety of psychosocial, socio-economic, and emotional concerns that may affect their daily lives.[12,13]

Hence, health status measures completed by patients themselves offer important supplements to traditional physician rated measures, with the incorporation of the patient perspective likely enhancing our understanding of the burden of disease and treatment on patients. Such patient reported outcomes may also be used in clinical decision making.[14,15] Recently, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that patients reporting more frequent angina complaints, assessed with the Seattle Angina Questionnaire,[16] derived the most benefit from percutaneous coronary intervention if also treated with optimal medical therapy.[17] These results testify to the utility of incorporating a measure of health status in research and clinical practice, as the patients with more severe angina complaints would likely not be identified based on the physician's judgment alone, in particular since physicians seem to underestimate the disability of patients.[18]

Besides impaired health status, ICD/CRT(-D) patients might experience heightened psychological distress and adjustment difficulties after implantation.[19] These psychological comorbidities are often underdiagnosed and undertreated in cardiology practice,[20] despite evidence showing that poor patient reported health status and distress have unique prognostic value as they are associated with premature death in cardiac patients, independent of demographic factors and indicators of disease severity despite treatment with state-of-the-art technology.[21-24] Hence, knowing which factors are associated with patient well being and psychological adaptation following ICD/CRT(-D) implantation is essential in the early identification and treatment of high-risk patients and may provide targets for secondary prevention.[25]

BROADEN THE SCOPE: THE IMPORTANCE OF PSYCHOLOGICAL FACTORS

As physician rated disease severity only explains some of the variance in patient reported outcomes, a logical next step is to look at the influence of factors specifically related to device therapy. So far, the evidence regarding the impact of these factors, e.g., ICD shocks,[26] indication,[27] and device advisory notices[28] is mixed. In general, findings from the current dissertation and previous research indicate that ICD/CRT patients are well able to cope with their device and experience low levels of device-related distress, even after being subjected to shock(s) or a device advisory notification (*Chapter 5*). However, a subset (20-30%) of patients might experience symptoms of depression, anxiety, and even posttraumatic stress (*Chapter 6*) following ICD/

CRT(-D) implantation.[19] In this dissertation, psychological factors were shown to be equal or more important associates of these psychological adjustment difficulties than disease severity and shocks. Pre-implantation anxiety and device concerns (C*hapter 6*), somatosensory amplification (*Chapter 7*), and poor device acceptance (*Chapter 1*0) were associated with heightened psychological distress following ICD implantation, independent of demographic and clinical factors. Also, Type D personality, a general propensity for distress, was shown to be associated with impaired physical and mental health status in cardiovascular patients (*Chapter 8*), and increased depression and anxiety levels (*Chapter 9*), posttraumatic stress (*Chapter 6*), and poor device acceptance (*Chapter 10*) in ICD patients. These findings are in line with previous studies emphasizing the importance of taking into account the psychological profile of the patient when seeking to identify patients at risk for poor patient reported outcomes post ICD/CRT-D implantation.[29-33] In particular, patients with a psychological vulnerability to experience distress (e.g., Type D personality, anxiety sensitivity, pre-implantation ICD concerns) seem to be at high risk for psychological adjustment difficulties, impaired health status and poor prognosis following implantation.[22,30-34] Hence, it may be timely for us to broaden our scope beyond factors related to disease severity and device therapy, and to also take into account psychological factors when studying patient reported outcomes in ICD/CRT(-D) patients. This is paramount to optimize patient centered care and to bridge the gap between research and clinical practice.[25] In the following sections, recommendations as to inclusion of the patient perspective in clinical practice and future research will be outlined (Table 1).

OVERCOMING THE BARRIERS OF IMPLEMENTING PATIENT REPORTED OUTCOMES IN CLINICAL PRACTICE

Patient reported outcomes are increasingly used as important outcome measures in clinical research trials on device therapy, such as the Canadian Implantable Defibrillator Study (CIDS), the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II).[35-37] However, their incorporation in clinical practice is far from standard due to practical, methodological, and attitudinal barriers.[38,39] Practical concerns include the general lack of time, money, and human resources to collect and analyze the data.[38] The use of new information infrastructures and computerized assessments might be one solution to mitigate these obstacles. For example, patients can complete the questionnaire at home or while waiting to see their physician using a touch screen computer. This information can then be added to the information from the medical history and physical examination at the initial and subsequent visits to the clinic.[40,41] However, sufficient technical support is required to make this feasible in the future.[42]

A methodological issue pertains to the choice of instrument to assess patient reported outcomes. Over the last decades, a number of health status measures have

been developed that are inexpensive, easy to administer, and psychometrically sound; it is important to choose the most appropriate and sensitive measure for the purpose at hand. Generic measures, such as the Short-Form Health Survey (SF-12 and -36),[43,44] are suitable for all populations and can be used to show differences in health status between cardiovascular patients and the general population or patients with another somatic disease. However, these measures may not be sufficiently sensitive to tap treatment-related changes.[45] The Minnesota Living with Heart Failure Questionnaire (MLHFQ)[46] and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[47] are disease-specific questionnaires specifically developed for use in CHF patients. These measures are often more relevant to patients and more accurate in reflecting clinical changes.[48] In addition, they seem to have greater prognostic value compared to health status assessed with a generic measure.[24] The Florida Patient Acceptance Survey (FPAS; *Chapter 10*),[49] Florida Shock Anxiety Scale (FSAS),[50] and the ICD Patient Concerns Questionnaire (ICDC)[51] are measures specifically developed to tap concerns and symptoms in ICD patients. It is important to assess patient reported outcomes at several time points as this allows for the rapid identification of patients whose health status deteriorates or whose distress levels increase or remain chronic following implantation.[14,15] Although there is a general reduction in distress in the first year after implantation,[52,53] in a substantial number of patients (50%) high levels of distress may persist over time.[54-57]

The next challenge is the analysis and interpretation of the scores. How much change in scores represents a meaningful improvement or deterioration in patient reported outcomes? Several studies have suggested a minimal magnitude of change for indicating clinical relevance (e.g., 5 points on the KCCQ[48]), and these cut off values can be used to classify patients into improved, stable, or deteriorated. If the proportions of patients who do or do not report improvement after an intervention is known, the number of patients needed to treat can be calculated.

Finally, the most challenging part of introducing patient reported outcomes into daily clinical practice is convincing the health care providers of their applicability and clinical usefulness.[14,38,42] Although most physicians seem to have positive attitudes towards using patient reported measures in daily practice, their attitudes seem to vary depending on their familiarity with these measures and the particular use to which they are put.[38,58] Preliminary evidence from family practice and oncology suggests that patient reported measures improve the physician's awareness of physical and psychological problems of patients and facilitate physician-patient communication,[38,41,58] which in turn may improve patient satisfaction and adherence to treatment.[5,14,59] Importantly, one study in cancer patients showed that the incorporation of patient reported outcomes in the clinical management of patients did not increase the time that physicians spend on patients in clinical practice.[58] Future research in cardiac populations is warranted to evaluate the most efficient way to use patient reported outcomes in clinical decision making in order to improve health

outcomes, such as mortality, morbidity, and quality of life.[14]

MANAGEMENT AND TREATMENT OF DISTRESSED PATIENTS

Once patients with poor patient reported outcomes are recognized in clinical practice and physicians have determined their specific concerns and health status impairments, appropriate interventions should be offered to improve health status – if this is possible – and to reduce their psychological distress levels.[60] So far, a paucity of studies have evaluated psychological and pharmacological interventions in device patients with the majority of these studies using cognitive behavioral therapy (CBT) as the mainstay of treatment.[61,62]

CBT includes training in cognitive-behavioral techniques (i.e., identifying and challenging negative automatic cognitions and behaviors), which is often combined with psycho-education about the underlying condition, the ICD/CRT(-D) device, and related misconceptions or concerns that are common among patients; relaxation and stress management techniques; and/or group sessions to promote social support. CBT was shown to significantly reduce psychological distress, in particular anxiety, and to improve health status in ICD patients.[63-69] Some studies have combined CBT with exercise training, with these multi-factorial interventions being more effective in reducing depression compared to CBT alone.[65,67,69] So far, no evidence is available to demonstrate a positive effect of psychosocial interventions on survival or recurrent cardiac events in ICD, probably due to the majority of these studies being based on relatively small sample sizes and having short follow-up periods.[61,62] Only one study documented an impact of CBT on use of health care facilities.[65] These preliminary findings suggest that psychological interventions are worthwhile in ICD patients, but also that large-scale, well-designed psychological intervention trials are warranted to confirm and expand on these findings.[61,62]

Psychopharmacological therapy might have supplemental value in reducing psychological distress. Selective serotonin reuptake inhibitors (SSRIs) appear preferable to treat distress in ICD/CRT patients, given their antidepressant and anxiolytic properties and their relatively benign (cardiac) side effects.[70-72] However, their efficacy in cardiac patients is not well known and some SSRIs might interact with other medications.[72,73] Hence, psychotropic medication should only be prescribed by physicians who know their specific effects in cardiac patients. Also, the patient's preference for psychological versus pharmacological treatment should be considered when offering a treatment, as a recent study in depressed primary care patients showed that receiving the preferred treatment might convey an additional and clinically relevant benefit.[74]

Finally, as addressed in *Chapter 9* of this dissertation, partners of ICD patients may experience levels of distress similar to patients,[75] which in turn may lead to 'overprotectiveness' and restriction of patient activities.[76] Hence, it is important for

health care professionals to be alert of the uncertainties and the distress of partners and provide them with adequate information and support.[76,77] This can be achieved by inviting partners to participate in cardiac rehabilitation where they can express their emotional and practical concerns but also witness that it is safe for ICD patients to exercise.[76,77]

KEEPING PACE WITH CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES - RECOMMENDATIONS FOR FUTURE RESEARCH

The incorporation of patient reported outcomes and the patient perspective in the cardiovascular implantable electronic device field is still in its infancy. Some ground has been gained, with such measures having been incorporated in primary and secondary prevention trials,[35-37] and with more and more observational studies taking an interest in the patient perspective and in how patients deal with the challenges of expanding indications, device advisory notifications, and ICD shocks (both appropriate and inappropriate) that go hand in hand with device therapy. However, most of these studies present mean group changes in patient reported outcomes, which could be misleading as there is a large variability in individual responses. The present dissertation provides more insight into the relative importance of disease- and device-related factors versus psychological factors in explaining variance in patient reported outcomes, nevertheless, a considerable number of questions still remain unanswered.

First, the complex nature of the psychological factors associated with patient reported outcomes needs further investigation. Most studies so far have focused on the individual impact of psychological factors, while these factors tend to cluster together within individuals.[30,78] For example, Pedersen and colleagues found that ICD patients with clustering of device-related concerns and Type D personality experienced higher levels of anxiety and had a poorer prognosis compared to patients with no or only one risk factor.[30,79] Hence, future research on psychological risk factor clustering might provide the most accurate risk estimation for individual patients rather than focusing on single factors.[78] Furthermore, it is important to enhance our understanding of the behavioral and biological pathways underlying the relationship between psychological factors and health outcomes, as this might point towards targets for secondary intervention. To confirm findings from observational studies, large-scale randomized controlled intervention trials targeting the psychological risk factors are essential. Such trials are also needed to determine which patients respond best to specific forms of psychological or pharmacological interventions, and to evaluate whether these interventions benefit prognosis in ICD/CRT patients. It is unlikely that a 'one size fits all' approach to intervention will work, requiring that interventions are targeted to the individual patient and their demographic, clinical, and psychological profile.

Second, well-designed studies are warranted examining factors specifically related to device therapy, e.g. shocks and advisory notices. Up until now, studies have yielded

mixed results and future research should adopt a more focused and standardized research approach in order to be able to draw firm conclusions about their impact on patient reported distress and health status.[26] The field of device therapy is also constantly evolving. The latest developments include remote monitoring of the device from the patients' home, new programming strategies in order to reduce the incidence of ICD shocks, and subcutaneous ICDs that have no leads inside or on the heart, which is expected to reduce the number of procedural- and device-related complications. The incorporation of patient reported outcomes in the clinical evaluation of these new technologies is paramount to identify patients who do not benefit optimally from new technology, as these patients may require adjunctive intervention.

Last but not least, most studies, including the ones in the current dissertation, indicate that ICD/CRT patients are generally well able to cope with their device, even after being subjected to shocks or device advisory notifications. Hence, it may be timely to shift our focus from poor patient reported outcomes to examining factors associated with positive adjustment after implantation, such as optimism and positive health expectations.[80] This is particularly important in light of the current debate in the scientific literature[81] and media[82] on the negative side effects of device therapy, with cardiologists being concerned that patients may turn down this potentially life-saving treatment. Cases of patients dying from sudden cardiac arrest that could have been prevented had they not refused an ICD have been reported in the US.[82] The incorporation of the patient perspective in research and clinical practice will enable physicians and other health-care professionals involved in the management and care of ICD/CRT(-D) patients to provide them with evidence-based information about what to expect from living with device, which in turn hopefully will counteract this negative publicity and prevent more unnecessary deaths. This was also voiced recently in the musings of Westby G. Fisher, internist, cardiologist and cardiac electrophysiologist: "So before our patients go out to buy funeral plots, let's keep the issues of the risks and benefits of ICD therapy, and the benefit or curse of their shocks, in perspective."[83]

Table 1. Recommendations for the incorporation of the patient perspective in clinical practice and future research in device practice

1) Recommendations for clinical practice

Assessment of patient reported outcomes

- Use disease-specific health status questionnaires, i.e. the Kansas City Cardiomyopathy Questionnaire (23 items), the Florida Patient Acceptance Survey (12/15 items) and the ICD Patient Concerns Questionnaire (8 items)
- Use (computerized) serial assessments

Management and treatment of distressed patients

- Attend to those patients whose health status does not improve or whose distress levels increase or remain chronic following implantation
- Offer these patients appropriate pharmacological and psychological interventions, such as cognitive behavioral therapy combined with exercise training
- Include a mental health professional who also knows about heart disease and device therapy in the multi-disciplinary staff that cares for patients; if this is not feasible, refer to a mental health professional outside the team
- Be alert of the concerns and distress of partners and include them in cardiac rehabilitation

2) Recommendations for future research

- Examine rapid and efficient ways to administer, score and interpret patient reported outcomes in clinical practice
- Identify the precise determinants of patient reported outcomes, taking (clustered) psychological factors into account
- Investigate the behavioral and biological pathways underlying the relationship between psychological factors and health outcomes
- Perform large-scale, well-designed intervention trials targeting psychological risk factors and/or underlying mechanisms
- Include patient reported outcomes in studies evaluating new device technologies

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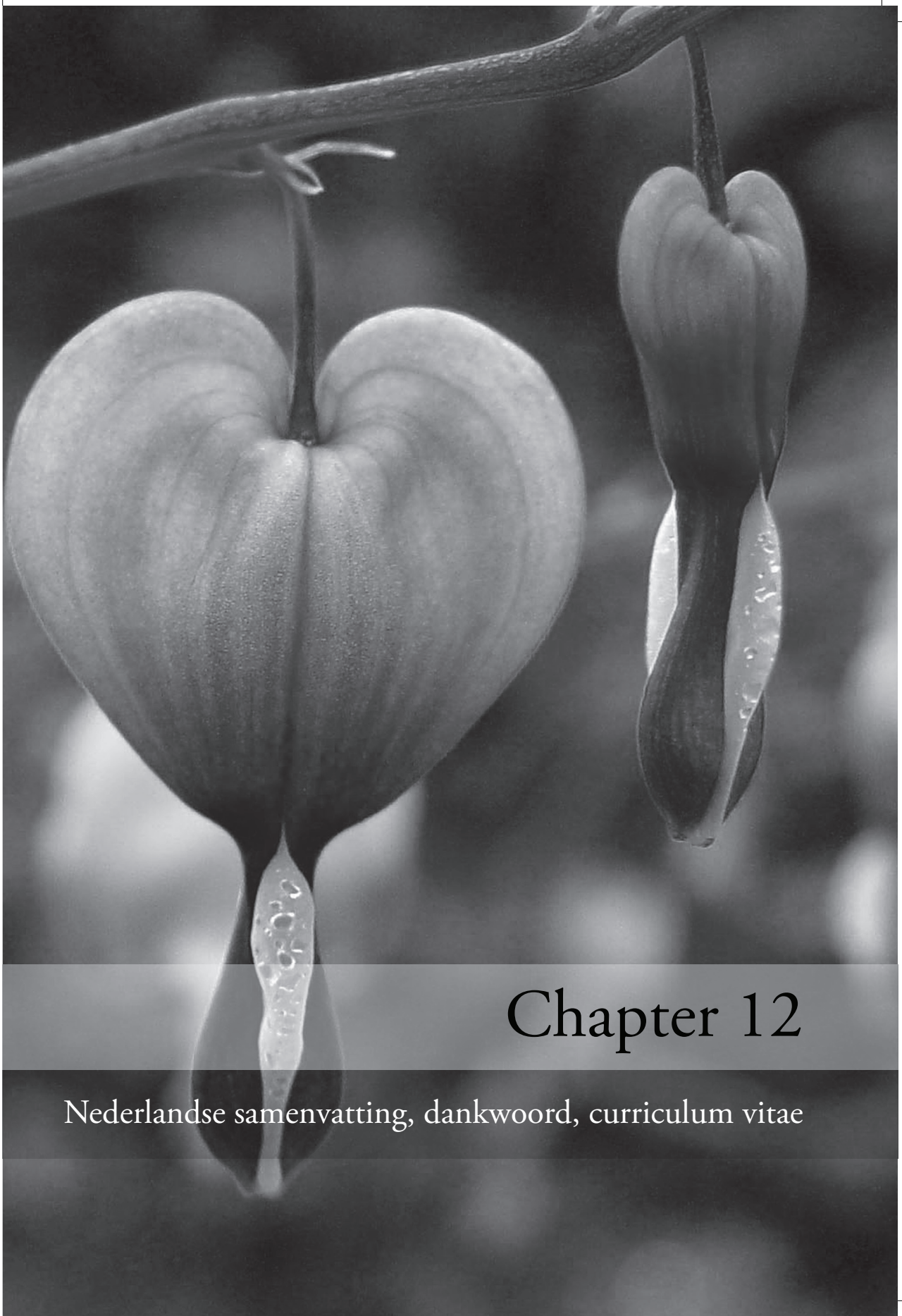


Chapter 12

Nederlandse samenvatting, dankwoord, curriculum vitae

NEDERLANDSE SAMENVATTING

Op dit moment leven er meer dan 800.000 hartpatiënten in Europa met een cardiovasculair implanteerbaar elektronisch systeem, zoals een implanteerbare cardioverter defibrillator (ICD) of een biventriculaire pacemaker die cardiale resynchronisatie therapie (CRT) afgeeft.

Een ICD wordt geïmplanteerd bij patiënten die ventriculaire ritmestoornissen hebben ervaren (secundaire preventie) of die, als gevolg van een structurele hartziekte, een verhoogd risico hebben op deze levensbedreigende ritmestoornissen (primaire preventie). De ICD registreert continu informatie over het hartritme via een geleidingsdraad (lead) in een of beide hartkamers (ventrikels). Als er een ritmestoornis wordt gedetecteerd, kan een ICD deze beëindigen door middel van snelle elektrische pulsen, zogenaamde antitachycardie pacing, of een elektrische schok en zo een eventuele plotse hartdood voorkomen.

Een biventriculaire pacemaker, of CRT-pacemaker, is bedoeld voor patiënten met mild tot ernstig hartfalen. Hartfalen kenmerkt zich door symptomen van vermoeidheid, kortademigheid en het vasthouden van vocht, veroorzaakt door een verminderde pompfunctie van het hart. Bij ongeveer 30% van de hartfalenpatiënten trekken de ventrikels vanwege een geleidingsstoornis niet gelijk samen waardoor de ventriculaire ejectiefractie (het percentage bloed dat bij één hartslag het lichaam ingepompt wordt) nog verder afneemt. Deze groep patiënten kan baat hebben bij CRT. Door kleine elektrische pulsen via een lead in de rechterventrikel en een op de wand van de linkerventrikel zorgt CRT ervoor dat beide ventrikels weer meer synchroon samentrekken. Bij het merendeel van de patiënten wordt er een derde lead in de rechterhartboezem (atrium) geplaatst zodat ook de synchronie tussen de ventrikels en atria verbetert. Omdat patiënten met hartfalen een verhoogd risico hebben op ritmestoornissen wordt een biventriculaire pacemaker, of een CRT-pacemaker, vaak gecombineerd met een ICD (CRT-defibrillator of CRT-D). Grootschalige internationale studies hebben aangetoond dat CRT bij de meeste patiënten leidt tot een verbeterde pompfunctie, een afname van hartfalensymptomen en een betere prognose. Naar aanleiding van studies als deze breiden de indicatiestellingen voor ICD en CRT therapie zich steeds verder uit en neemt het aantal hartpatiënten met een ICD of CRT systeem snel toe.

DOEL VAN DIT PROEFSCHRIFT

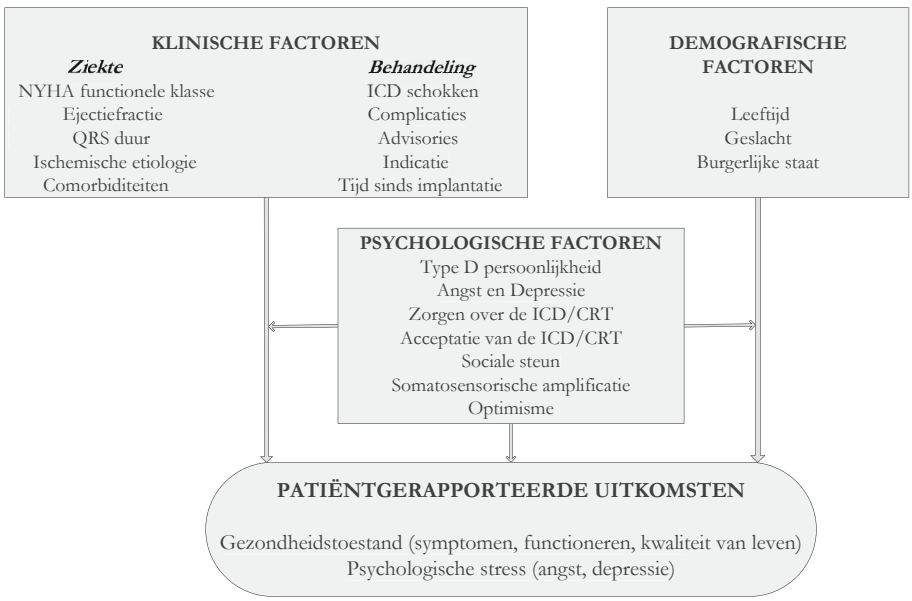
In onderzoek en de klinische praktijk wordt vaak aangenomen dat elke behandeling die de overlevingskansen verbetert ook goed moet zijn voor de patiënt en dat alle patiënten dezelfde verbeteringen in hun fysieke en mentale welbevinden ervaren. Het leven met een ICD of CRT(-D) wordt echter door iedere patiënt anders beleefd. Om een beter beeld te krijgen van de gevoelens en ervaringen van patiënten lag de focus van dit proefschrift op zogenaamde patiëntgerapporteerde uitkomsten. Patiëntgerapporteerde

uitkomsten zijn uitkomsten van vragenlijsten die door patiënten zelf worden ingevuld. Deze lijsten gaan bijvoorbeeld over de symptomen die patiënten ervaren, hun lichamelijk en mentaal functioneren en hun kwaliteit van leven. Ze geven inzicht in hoe patiënten zelf hun gezondheid waarderen (hun subjectieve gezondheidstoestand) en hoe zij psychologisch gezien omgaan met hun ziekte en/of de behandeling.

Uit eerdere onderzoeken is gebleken dat ongeveer 1 op de 4 ICD dragers na de implantatie angstige en depressieve gevoelens en/of een verminderde kwaliteit van leven rapporteert. Er bestaat echter nog veel onduidelijkheid over de oorzaken van deze gevoelens. Het is belangrijk om dit verder te onderzoeken, zodat we kunnen voorspellen welke patiënten een hoog risico lopen op negatieve patiëntgerapporteerde uitkomsten na de implantatie. Aan deze patiënten kan dan tijdig extra (psychologische) hulp worden geboden om te voorkomen dat hun subjectieve welzijn verder achteruit gaat. Dit kan ook belangrijk zijn voor secundaire preventie, omdat is aangetoond dat patiëntgerapporteerde psychologische stress en een slechte subjectieve gezondheidstoestand samenhangen met een verhoogd risico op ziekenhuisopnames of overlijden.

Het doel van dit proefschrift was om een beter beeld te krijgen van de factoren die samenhangen met individuele verschillen in patiëntgerapporteerde uitkomsten. Figuur 1 geeft een overzicht van klinische, demografische en psychologische factoren die van belang zouden kunnen zijn. In de negen studies in dit proefschrift is het verband tussen enkele van deze factoren en patiëntgerapporteerde uitkomsten onderzocht in steekproeven van ICD of CRT(-D) patiënten uit verschillende (inter)nationale ziekenhuizen.

Figuur 1. Factoren die (mogelijk) samenhangen met patiëntgerapporteerde uitkomsten



VOORNAAMSTE BEVINDINGEN VAN DIT PROEFSCHRIFT

Hartfalen is een chronische en slopende ziekte die een grote invloed kan hebben op het dagelijks leven van patiënten. In de medische wereld wordt vaak aangenomen dat het subjectieve welzijn van een patiënt vooral wordt bepaald door de ernst van de ziekte. In de eerste drie studies in dit proefschrift bekeken we daarom het verband tussen de subjectieve, patiëntgerapporteerde gezondheidstoestand en de traditionele 'objectieve' maatstaven die cardiologen gebruiken om de ernst van het hartfalen te beoordelen, zoals echoparameters en de New York Heart Association (NYHA) functionele klasse. De NYHA klasse is een classificatie voor de ernst van hartfalensymptomen en functionele beperkingen zoals die wordt ingeschat door de arts: hoe hoger de klasse (I t/m IV), hoe ernstiger het hartfalen. De NYHA klasse is een van de meest gebruikte maten waarop de keuze van een behandeling voor hartfalen wordt gebaseerd en het succes daarvan wordt beoordeeld. Uit de bestaande literatuur en ervaringen uit de dagelijkse praktijk blijkt echter dat er nauwelijks verband bestaat tussen deze klinische maatstaven voor de ernst van het hartfalen en de gezondheidstoestand die de patiënt zelf rapporteert (*Hoofdstuk 2*). Zo zijn er patiënten bij wie het hartfalen volgens de resultaten van de hartecho, de inspanningstest en/of het laboratoriumonderzoek is verbeterd, maar die zelf geen verbetering ervaren, of andersom. Deze discrepantie wordt bevestigd in de studies beschreven in Hoofdstuk 3 en 4 van dit proefschrift. Zo bleek dat de verandering in de subjectieve gezondheidstoestand na de CRT-D implantatie niet verklaard kan worden door de NYHA klasse bij implantatie (*Hoofdstuk 3*). Patiënten met mild (NYHA klasse II) en matig ernstig (NYHA klasse III) hartfalen bij implantatie rapporteerden 12 maanden later gelijke verbeteringen op subjectieve gezondheidsdomeinen zoals fysiek en sociaal functioneren en mentale gezondheid. In de andere studie hebben we bij 101 CRT(-D) patiënten gekeken naar hun gezondheidstoestand voorafgaand aan de implantatie en 2 maanden daarna (*Hoofdstuk 4*). Bij 59 patiënten was er geen verbetering van het hartfalen volgens de NYHA klasse, maar toch rapporteerden 36 van deze 59 patiënten (61%) een klinisch relevante verbetering in hun gezondheidstoestand op een hartfalen-vragenlijst. Deze resultaten benadrukken dat patiëntgerapporteerde vragenlijsten een meerwaarde hebben voor de inschatting van de ernst van het hartfalen vanuit het perspectief van de patiënt in vergelijking met de traditionele functie-indeling in NYHA klassen.

Uit bovenstaande resultaten blijkt dat het subjectieve welzijn van patiënten slechts voor een deel verband houdt met de ernst van het hartfalen volgens klinische maatstaven. ICD en CRT patiënten worden echter niet alleen geconfronteerd met de gevolgen van hun ziekte, maar ook met de uitdagingen die horen bij het leven met een ICD/CRT systeem. De complexiteit van de ICD en CRT technologie maakt dat deze gevoelig is voor complicaties, zoals hardwareproblemen. Een recent voorbeeld hiervan zijn de problemen met de Sprint Fidelis lead van Medtronic. In 2007 kwam het waarschuwingsbericht (advisory) naar buiten dat de kans op breuken bij deze

specifieke lead groter is dan bij andere Medtronic leads. Een dergelijk bericht zou angstgevoelens en zorgen kunnen veroorzaken bij patiënten met een Sprint Fidelis lead. In een studie van Deense ICD patiënten (*Hoofdstuk 5*) vonden wij echter dat patiënten met een Sprint Fidelis lead gemiddeld genomen niet méér psychologische problemen of een slechtere kwaliteit van leven rapporteerden dan controlepatiënten zonder deze Sprint Fidelis lead. Ook de manier waarop de patiënten van de Sprint Fidelis advisory hoorden, via een brief met een oproep om direct voor controle naar het ziekenhuis te komen of tijdens een routinecontrole op de polikliniek, had geen invloed op patiëntgerapporteerde uitkomsten. Deze bevindingen sluiten aan bij eerdere studies die eveneens aantonen dat patiënten over het algemeen goed omgaan met hun ICD en weinig psychologische stress ervaren, zelfs na het krijgen van ICD schokken of een advisory.

Patiënten met negatieve patiëntgerapporteerde uitkomsten zijn dus niet per definitie die patiënten die ernstiger ziek zijn en/of meer behandelingscomplicaties hebben doorgemaakt. Uit de studies in deel twee van dit proefschrift bleek dat het psychologische profiel van patiënten ook een belangrijke rol speelt. Zo waren angst en bezorgdheid over de ICD voorafgaand aan de implantatie (*Hoofdstuk 6*), somatosensorische amplificatie (*Hoofdstuk 7*) en een slechte acceptatie van de ICD (*Hoofdstuk 10*) geassocieerd met verhoogde psychologische stress na implantatie, onafhankelijk van demografische en klinische factoren als NYHA klasse en ICD schokken. Somatosensorische amplificatie wordt gekenmerkt door een overdreven aandacht voor bepaalde normale lichamelijke sensaties en de neiging om op deze sensaties te reageren met gedachten die ze versterken en verontrustender maken. Ook persoonlijkheidsfactoren kunnen een rol spelen in individuele verschillen in patiëntgerapporteerde uitkomsten. Zo liet een meta-analyse van 10 studies (*Hoofdstuk 8*) zien dat de 'distressed' (Type D) persoonlijkheid samenhangt met een slechtere subjectieve mentale en fysieke gezondheidstoestand bij verschillende cardiovasculaire patiëntengroepen. Individuen met een Type D persoonlijkheid ervaren veel negatieve emoties en maken zich veel zorgen, maar uiten hun gevoelens en emoties niet naar anderen. De studies in dit proefschrift toonden aan dat ICD patiënten met een Type D persoonlijkheid meer symptomen van angst, depressie (*Hoofdstuk 9*), posttraumatische stress (*Hoofdstuk 6)* en een slechtere acceptatie van de ICD (*Hoofdstuk 10*) rapporteerden dan patiënten zonder het Type D persoonlijkheidstype.

CONCLUSIES EN AANBEVELINGEN

De bevindingen in dit proefschrift bevestigen eerdere studieresultaten dat patiëntgerapporteerde uitkomsten in dezelfde of zelfs sterkere mate samenhangen met het psychologisch profiel van de patiënten dan met de ernst van hun ziekte of behandelingscomplicaties. Het subjectieve welzijn van een patiënt is dus niet direct af te leiden uit de gegevens in zijn/haar medische dossier. Daarom hebben vragenlijsten

die het perspectief van de patiënt meten een meerwaarde voor onderzoek en in de klinische praktijk.

Patiëntgerapporteerde uitkomsten worden in toenemende mate meegenomen in onderzoeken naar de effecten van ICD/CRT(-D) therapie, maar hun toepassing in de dagelijkse klinische praktijk is verre van standaard, vooral vanwege praktische bezwaren. Er is immers geld, tijd en personeel nodig om de gegevens te verzamelen en te analyseren. Toch is het de moeite waard om meer onderzoek te doen naar een efficiënt en goedkoop gebruik van vragenlijsten in de cardiologische praktijk. Studies bij kankerpatiënten hebben namelijk aangetoond dat artsen door patiëntgerapporteerde uitkomsten een beter inzicht krijgen in de specifieke lichamelijke en psychologische behoeften van patiënten. Dit kan vervolgens bijdragen tot een betere communicatie tussen arts en patiënt, een hogere patiënttevredenheid en betere patiëntgerichte zorg. Door vragenlijsten op meerdere momenten af te nemen kunnen patiënten die psychologische stress ervaren rond de implantatie of bij wie het subjectieve welzijn achteruit gaat eenvoudig(er) worden geïdentificeerd. Vervolgens is het belangrijk dat deze patiënten de juiste hulp krijgen aangeboden, afgestemd op hun individuele behoeften. Zo zouden angstige patiënten bijvoorbeeld baat kunnen hebben bij cognitieve gedragstherapie.

Om de interventies zo goed mogelijk af te stemmen op de behoeften van de individuele patiënt is meer onderzoek nodig naar de complexe invloed van psychologische factoren en de gedragsmatige en biologische mechanismen die hieraan ten grondslag liggen. Daarnaast zijn er grootschalige en gestandaardiseerde studies nodig naar de impact van nieuwe ontwikkelingen binnen de ICD/CRT technologie op patiëntgerapporteerde uitkomsten. De meest recente ontwikkelingen zijn het op afstand monitoren (remote monitoring) van de ICD/CRT(-D) waardoor patiënten minder vaak voor controle naar het ziekenhuis hoeven te komen, nieuwe programmeerstrategieën om het aantal ICD schokken te verlagen en de subcutane ICD die geen leads in of op het hart heeft. Bij het evalueren van deze ontwikkelingen is het essentieel om patiëntgerapporteerde uitkomsten mee te nemen zodat beter kan worden voorspeld welke patiënten er wel of geen baat bij zullen hebben.

Tenslotte, over het algemeen blijkt dat de meeste patiënten goed omgaan met hun ICD/CRT-D) en weinig psychologische stress of aanpassingsproblemen ervaren. Daarom is het wellicht tijd om de focus te verleggen naar positieve patiëntgerapporteerde uitkomsten en de factoren die hiermee samenhangen, zoals optimisme. Dit is vooral belangrijk in het licht van de huidige discussie in de wetenschap en de media over de eventuele negatieve bijwerkingen van ICD therapie waardoor sommige patiënten deze levensreddende behandeling afwijzen. Door het perspectief van de patiënt mee te nemen in onderzoek en de klinische praktijk kunnen zorgverleners hun patiënten goed onderbouwde en reële informatie geven over wat ze kunnen verwachten van het leven met een ICD of CRT(-D).

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